A.M.A. Archives of
INTERNAL MEDICINE

OCTOBER 1956

VOLUME 98 NUMBER 4

The Natural History of Disease
William S. Middleton

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Lawrence Peters

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Loeffler's Syndrome with Cardiac Involvement *John T. Leckert*

The Syndrome of Pseudo-Pseudohypoparathyroidism
Stanley Wallach, Edwin Englert Jr., and Harold Brown

Hepatitis Complicating Mumps
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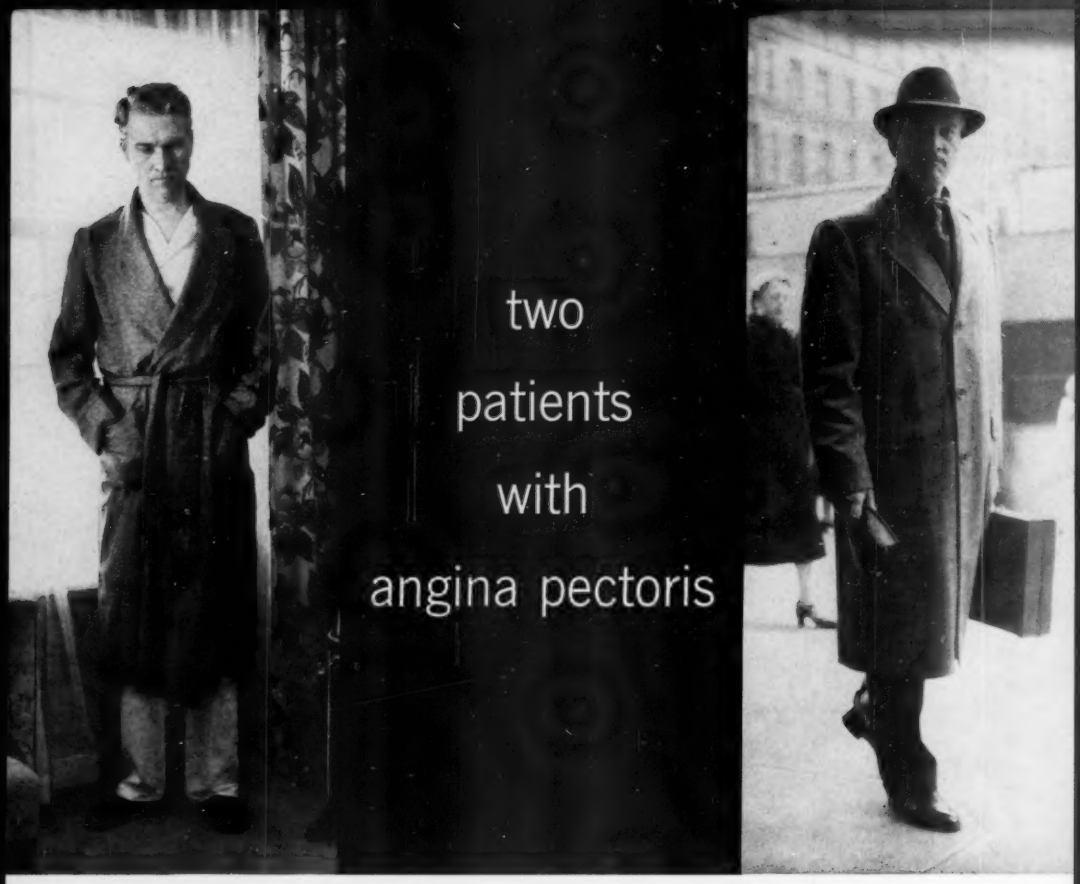

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TO OUR SUBSCRIBERS AND CONTRIBUTORS

SUBSCRIBERS and contributors to this journal have undoubtedly noticed some deviation from our usual publishing quality in the July and August and September issues. In particular, authors have had to correct very bad proofs in less than adequate time for careful reading. Subscribers must have detected an unusual number of typographical errors which were not corrected from the galleys. A most disturbing fact was the late mailing of these issues. Many of our authors and readers were quick to realize that such a departure from our usual standards could be due only to abnormal conditions, and we feel that these conditions need to be explained.

On April 23, 1956, the American Medical Association concluded negotiations for a contract with the Baird-Ward Printing Company, Inc., Nashville, Tenn., to print the American Medical Association Specialty Journals. Under the terms of the contract, the Baird-Ward Printing Company, Inc., was to begin with the July issues.

A transfer of a printing operation requires that many details be considered and many adjustments be made. A contract as large as this involved expanding a work force with skilled operators, not always readily available; installing additional machinery and type equipment not obtainable on short notice, and scheduling nine journals so as to coordinate their production with other jobs in the plant. Editorially, it meant increased pressure upon editors to meet an advanced schedule, the development of a common interpretation of editing procedures between typesetter and manuscript editor, and the working out of communications between the Editorial Office, printing plant, authors, and readers.

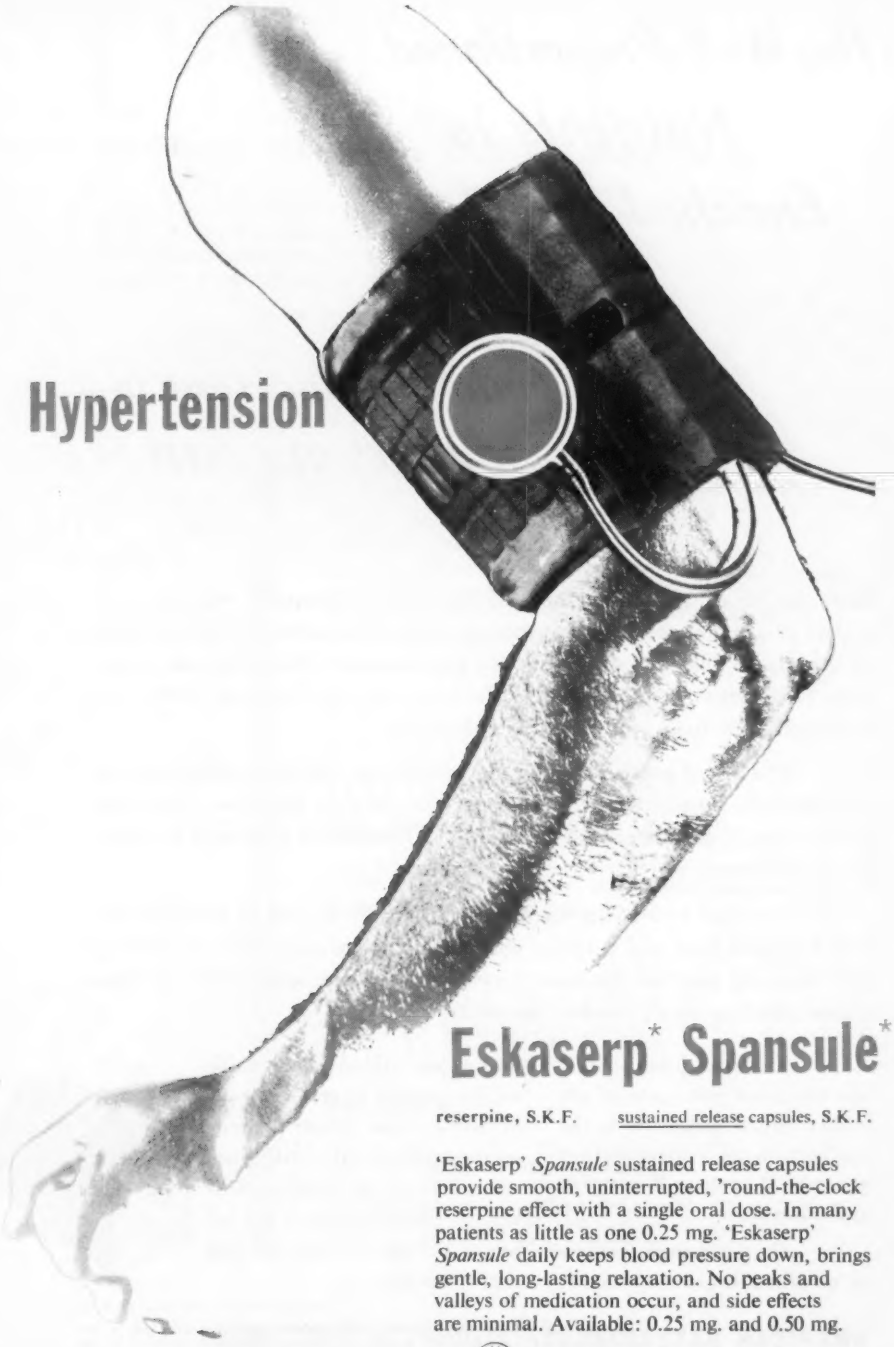
All this was a Herculean task in view of the short period of time allowed for the transfer. Obviously, substandard results could not be avoided. While a contributor or a reader is justly concerned with his individual article or copy, it is hoped that the realization of the many ramifications of the transfer will soften criticism of the initial effort, performed under an entirely new set of production conditions.

Many of the early problems have been eliminated. Others are being solved daily. The efforts of the editorial and manufacturing staffs are directed toward an improvement over what our readers have been offered in the past. Publication dates will be improved, and plans are progressing to make our subject contribution more essential to the profession.

We trust that a better understanding of the circumstances will enlist your patient indulgence in our efforts to return to normal publishing conditions and to keep a promise of a better product.

MANAGING EDITOR

Hypertension



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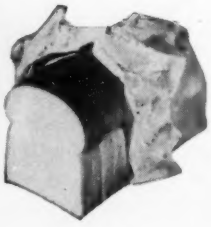

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Editorials

MOTORING

A Clinical Challenge

AN EXPANDING knowledge of the clinical life history of motorists clearly indicates that rider injuries and deaths implicate the entire field of clinical medicine, not the surgical specialties alone. Once that statement is accepted, its real meaning becomes evident, i. e., that the internists should be members of the teams that treat automobile casualties. Afterward, the internist will go further and identify himself just as specifically with problems of accident prevention, reduction of injuries under crash conditions, and medicolegal problems.

In the first place, the mortality from rider injuries occurs in a small but lethal group of casualties, estimated to be about 10% of the total number who are injured badly enough to require hospitalization. Why these people die is revealed chiefly from studies made at autopsy—in the good old-fashioned way (which seems to be losing ground and caste in these days of high-powered ideas regarding the value of such methods of collecting scientific medical data).

About 85% of these people die after they reach the hospital; only 15% die at the scene of the accident. Moreover, a large per cent die shortly after admission (about one-third); about another third die within 48 hours after admission, and the remainder some time afterward (usually in the first week or two). In other words, about one-half of the deaths result after sufficient time has elapsed for definitive diagnosis and treatment. Here is the actual area for participation by the internists. The cumulative effects of both primary injuries and complications are best considered from the standpoint of secondary shock. Already, but 12 hours after admission, such conditions as fat embolism, pneumonia, lower nephron nephrosis, hyperpyrexia, and unexplained shock-like states had contributed to the deaths of these persons. In the later fatalities, similar situations, in addition to infectious conditions, played an important role.

The most convincing argument favoring participation of internists on any team treating automobile casualties derives from two very cogent observations at autopsy: (1) that at least 50% of the internal injuries are contusive rather than lacerative (and usually require surgical intervention); (2) that about one-third of the deaths show injuries to the mediastinum (cardiac, pericardial, and great vessels).*

Also, observations on a large number of injuries in survivors again emphasizes the fact that cardiorespiratory situations are becoming increasingly more numerous

Received for publication June 21, 1955.

*Based on 29 autopsies.

and more challenging from the therapeutic standpoint as well as diagnosis. In point of fact, the mere multiplicity of injuries and complications—in a large proportion of automobile casualties (about 45%)—demand the services of an internist to aid as well as to help guide the surgeon in regard to assessment of therapeutic priorities.

Having observed the seriousness of some automobile injuries, the internists will turn their attention to an even more promising aspect—that of accident prevention through better medical standards of driver licensure and the maintenance of driver fitness. The domain of driver licensure is largely that of the internist. This is especially significant from the standpoint of considerations of the driver under therapeutic medication (tranquilizers, etc.).

Regarding the reduction of injuries under crash conditions and/or decelerative upsets, the internists could offer much of interest to automotive engineers and automotive designers, especially in regard to chest and mediastinal injuries, as well as upper abdominal ones (rare though the latter are).

Finally, there is a large field of thought and endeavor in the medicolegal residues for the internist, who has, perhaps, remained aloof for too long a period from this battleground already. The increasing number of chest injuries and the increasing number of older people who are becoming involved in automobile accidents is invitation enough for the civic-minded internist.

The realization that automobile casualties are on the increase (gross numerically); that causation is multiple, and that diagnosis and treatment is complex, all demand a multifaceted approach to its control and/or reduction. From the clinical standpoint, all branches of medicine and surgery must take a more active part in this effort. However, the area which begs for further development seems to be in the domain of internal medicine. This is not the same as saying that internal medicine has been incapable of coping with its own particular segment of the problem. Simply stated, it does mean that for one reason or another, the internist does not become a part of any team that treats these injuries frequently enough. This is obvious from any study of the hospital records. This sort of a situation is not in the best interests of the crash victims and undoubtedly has resulted from an unawareness—on the part of both surgeon and internist alike—of the effective role that the internist could play in this clinical activity were he given the best opportunities to help, i. e., from the very beginning of the patient's care, when baseline studies should be made. Internists ought not to be hesitant about offering their talents to these problems at hospital staff meetings, and, what is more to the point, surgeons should seek the help of internists more frequently and earlier in the patient's hospital stay. Be that as it may, internist and surgeon, general practitioner and specialist, had better bend every effort toward helping to solve some of the challenges to our public and individual safety and health which the automobile accident continues to present in ever-increasing numbers every year.

JACOB KULOWSKI, M.D.
415 Corby Bldg., St. Joseph, Mo.

The Natural History of Disease

Frank Billings Memorial Lecture

WILLIAM S. MIDDLETON, M.D., Washington, D. C.

Appropriately, we are met today to honor the memory of a great clinician and medical statesman, Frank Billings, in Chicago, where his fine professional stature and eminence were attained. In 1878, a sturdy farm lad from Iowa County, Wisconsin, matriculated in the Chicago Medical College (now Northwestern University Medical School). Of splendid Anglo-Saxon stock, he was superbly endowed physically and intellectually. Upon completion of a common public school education, young Billings had attended the Platteville (Wisconsin) State Normal School for two years. Thereafter, he taught a country school in the town of Eden. His prompt advancement to the principalship of the Platteville High School was, in retrospect, a true forecast of his driving ambition and capacity.

Upon graduation from the Chicago Medical College, Dr. Billings served an internship in Cook County Hospital, a coveted post for the young physicians of that period. The investment of postgraduate studies in London, Paris, and Vienna gave his career an impetus that brought him shortly to the forefront of medicine in Chicago. Aside from Dr. Billings' personal attributes, his activities in the introduction of laboratory methods into clinical practice were probably the "open-sesame" to his initial success that eventually carried him to a position of preeminence in American medicine.

Dr. Billings was a born leader. He literally dominated every gathering he attended by the force of his presence and personality. Both at Northwestern University Medical School and at Rush Medical College, his efforts brought fruit in the improvement and the expansion of the physical plants. He was particularly effective in enlisting the financial support of wealthy Chicagoans in medical philanthropy. From his vantage point, Dr. Billings led the attack on nostrums and subnormal medical schools. The Council on Pharmacy and Chemistry and the Council on Medical Education and Hospitals of the American Medical Association were natural products of his energetic representations. His thoughts on medical education were especially advanced in the advocacy of the utilization of full and part-time clinical teachers in an integrated program. His recommendations for the coordination of public and private hospitals in a teaching plan are still valid and might be reviewed with profit in the light of a changing picture. With characteristic prescience, Dr. Billings urged the establishment of a national examining board.

Lest the erroneous impression of an impersonal austerity be gathered from this recital of achievements, it should be recorded that Dr. Frank Billings was fundamentally a warm, kindly man. Physically massive, he was just as large of heart. Out of the abundance of his life and substance he gave unstintingly to every worthy cause. The connotation of the term "builder" that is so regularly applied to Dr. Billings in this community may deprive posterity of a measure of the deep humanity of the man. Rarely are the dominant qualities of ac-

Submitted for publication June 12, 1956.

Chief Medical Director, Department of Medicine and Surgery, Veterans Administration.

This paper is being published simultaneously in the *Journal of the American Medical Association*.

Read before the Section on Internal Medicine at the 105th Annual Meeting of the American Medical Association, Chicago, June 12, 1956.

cepted leadership so blended with the depth of human sympathy that characterized him. His students, nurses, interns, and associates adored him. Dr. Billings died in his 79th year (Sept. 20, 1932). His memory is held in reverence by a host of friends, both lay and professional, who were privileged to associate with him in his manifold activities.

Development of the Study of Disease

Health is no longer viewed in the negative sense as the mere absence of disease. Health connotes a harmony of mind and body with self and environment. This balance will obtain with the normal activity of every vital and supporting function. The nice adjustments of the body to its surroundings have been grouped under the term homeostasis by Cannon. Selye has extended this concept in his theory of adaptation. The internal milieu of the mammalian body is a complex, ever-changing medium of physical, physiological, and chemical factors so integrated in health as to maintain a sense and a presence of well-being. The present viewpoint, for example, emphasizes the continuous alterations in chemical constituents upon momentary changes in bodily or tissue requirements. Such changes may involve simple chemical reactions, or they may invoke complex physical, enzymatic, and steroid mechanisms. As long as the reserve of the involved elements is adequate, physiological equilibrium may be maintained. To this harmonious balance, the term eucrasia (eucrasy) has been applied.[1] An unnatural imbalance through an exhaustion of the reserves or an inability to meet demands from normal or abnormal sources results in a disturbance of function. Such disruptions find expression in symptoms and eventually in signs arising from pathological changes in tissues or organs.

From the beginning of recorded time, man has endeavored to interpret the manifestations of disordered function. The concepts reflect the state of human knowledge of a given period. From time to time, medical advance has been impeded by attempts to apply rigid criteria in the grouping of diseases. Nosology has, on occasions, been viewed as an end rather than an instrument in our hands. Indeed, systems of practice have been built on such insecure foundations. With the ascendancy of morbid anatomy and the splendid dividends from clinical-pathological correlations in the early 19th century, "dead-house" medicine dominated the scene for a period. In fact, in certain quarters no diagnosis was complete without the autopsy findings! Microbiology came into high estate in the late 19th and early 20th centuries. With its rise came the clinical fixation upon etiology. The last three decades have witnessed an upward surge in the physiological and the physiological-chemical knowledge of bodily reactions in health and disease. The impact of physical, physiological, steroid, enzyme, and nuclear physical-chemical observations on medical thought and practice has been stupendous in recent years and will increase.

In this advance, medicine must never lose sight of fundamental facts. Sydenham[2] wrote, "A disease in my opinion, how prejudicial soever its cause may be to the body, is *no more than a vigorous effort of nature* to throw off the morbific matter, and thus recover the patient." In this light, disease must not be considered as an isolated phenomenon nor a series of more or less related phenomena. Man is rarely the passive host of "morbific matter" but reacts more or less violently, dependent upon the nature of the alteration induced locally or generally. Regardless of whether the inciting factor be microbial, nutritional, metabolic, degenerative, or neoplastic, there are always contributing circumstances in the evolution of the state of inequilibrium termed disease that must be given due consideration in the true comprehension of its natural history.

Within the memory of many physicians still active in the practice of medicine, there have been many radical changes in the mode of infectious diseases and in the clinical expression of specific infections.

The exanthems are waning in incidence and severity. Black measles, black scarlet fever, and black smallpox are now only terrifying memories. Diphtheria, with its toll of morbidity and mortality, is largely controlled. Typhoid no longer recurs each summer and autumn to reflect the limitations of sanitation and the contamination of the water (and milk) supply. Lobar pneumonia is a rarity in our teaching hospitals. Suppurative mastoiditis and empyema are relics of a past that medicine would forget. Tuberculosis is losing some of its terror, but it is by no means a vanquished threat to health and life. Syphilis and gonorrhea are more adequately treated than ever before, but the failure to eradicate these diseases reflects the limitations of purely curative medicine. Moreover, man is paying a penalty for the disruption of the biological balance of nature through the introduction of antimicrobial agents. Resistant strains of pathogenic bacteria are appearing. Rickettsial and viral infections have increased with the abatement of bacterial diseases. With the change in the flora of the body under antimicrobial therapy, fungal infections have emerged in increasing frequence.

Observation and Experimentation

The time for reflection is now at hand. Before the countenance of certain of these diseases has vanished from the earth, we must attempt to commit to the printed record every detail of their course. At best, our observations are fragmentary. The published accounts of diseases too frequently represent the subjective reports of the patient, supplemented by the periodic examinations of the physician. From these bits and pieces, a composite picture is reconstructed. This reproduction is frequently at variance with the autobiographic accounts of physicians suffering from the same disorder. Sydenham's [2] account of his own gouty attacks is a classic example of this truth. A physician should be a "minister (or servant) and interpreter of nature" (Hippocrates). By observation and experimentation, medicine must strive to fill the gaps in a comprehensive understanding of the natural history of disease.

Sir Thomas Lewis,[3] while deploring the cleavage, bespoke the separate training of physicians for clinical medicine and for clinical science: "This science seeks, by observation and otherwise, to define diseases as these occur in man; it attempts to understand these diseases and their many manifestations and, here especially, makes frequent use of the experimental method." In his evolution of the thesis, Lewis indicated that two different types of psychological attributes were involved: "Self-confidence is, by general consent, one of the essentials to the practice of medicine, for it breeds confidence, faith and hope. Diffidence, by equally general consent, is an essential quality in investigation, for it breeds inquiry." Obviously, an acceptance of this position would spell a sharp limitation to the observational approach of which Lewis stated, "Eventually, however, the fertility of this method greatly declines by a process of exhaustion and, for those who can read the signs, this time has come in medicine." Trotter [4] voiced a similar reservation thus: "This limitation is the circumstance that the observer must wait upon the natural occurrence of the phenomena he wishes to study. The phenomena may be too infrequent for their significant recurrence to come within the span of human life, they may be too complex and too closely mixed with irrelevant events for the invariable sequence they possess to be detected."

Actually, the contention that observational and experimental skills are incompatible is untenable. The ramifications of the scientific approaches to the study of man in health and disease exceed the capacity of any physician to encompass, much less to apply them to the multitudinous clinical problems with which he is confronted. Wherever possible, these scientific methods must be invoked in the elucidation of covert situations, but a proper sense of proportions must be preserved. Mackenzie [5]

said, "When I see the modern cardiologist getting his assistant to take an x-ray photograph of the heart and electrocardiogram, and even a blood-pressure reading, and then behold him sitting down to study these reports, I am truly amazed. I never could have realized that the practice of medicine could have become so futile and ineffective." Certain of the random chemical probings in the guise of medical practice are even more astounding. Without depreciating these studies one iota, let it be clearly understood that the only individual competent to direct the care of the patient is the physician. If he be wise, he will welcome the support of his associates in the basic sciences for coordinate clinical study. From their joint efforts will come a more complete understanding of the patient's problems and more intelligent treatment.

Indeed, out of such cooperative efforts have come material advances in the clinical appreciation of certain disorders in very recent years. Pheochromocytoma was a poorly understood neoplasm until physiologists and pharmacologists clarified the background. Aldosteronism emerged as a distinct clinical entity upon the definition of its steroid responsibility. Agammaglobulinemia awaited electrophoretic fractionation of the serum protein for elucidation of the attendant recurring infections. The unusual symptoms and signs attendant upon carcinoid of the intestinal tract with hepatic metastasis represent an extraordinary example of the interdependence of observation and experimentation in the explanation of disordered function. With Charcot we may say, "Disease is from of old and nothing about it has changed. It is we who change, as we learn to recognize what was formerly imperceptible."

Hence, it behooves the physician to preserve his clinical acumen, as he accepts and extends the application of newer laboratory methods to the study of his patients. Indeed, his position must be fortified from a psychological standpoint to avoid the impersonality of the laboratory. If the physician is to capitalize on this advantage, however, the time is ripe for a new approach to the natural history of disease. With due attention to the experimental and laboratory contribution to this vital subject, there remains a vast area for reexploration and inquiry. John Brown [6] wrote, "Symptoms are universally available; they are the voices of nature." Mackenzie [5] said, "When we search for the recondite and the obscure, we fail to recognize the simple and the obvious." The English school has produced a number of great clinicians in the Hippocratic pattern. Thomas Sydenham [2] said:

> In writing, therefore, a history of diseases, every philosophical hypothesis which hath prepossessed the writer in its favor, ought to be laid aside, and then the manifest and natural phenomena of diseases, however minute, must be noted with utmost accuracy, imitating in this the great exactness of painters, who in their pictures copy the smallest spots or moles in the originals; for it is difficult to give a detail of the numerous errors that spring from hypothesis.

Thomas Willis [7] was a true seeker for knowledge, as witnessed in the following statement:

> After I had not found in Books what might satisfy a mind desirous of truth, I resolved with myself to reach into living and breathing examples: and therefore sitting oftentimes by the Sick, I was wont carefully to search out their cases, to weigh all the symptoms and to put them, with exact Diaries of the Diseases into writing; then diligently to meditate on these; and then begin to adapt general notions from particular events.

In a similar spirit, William Heberden [8] afforded the following plan:

> The notes, from which the following observations were collected, were taken in the chambers of the sick from themselves, or from their attendants, where several things might occasion the omission of some material circumstances. These notes were read over every month and such facts as tended to throw any light upon the history of a distemper or the effects of a remedy, were entered under the title of the distemper in another book, from which were extracted all the particulars here given relating to the nature and cure of diseases.

Heberden's account of diabetes [8] serves as an example of the application of his method:

> An unusual thirst is first taken notice of, with

a tongue rough and furred, and a bad taste in the mouth; the appetite fails; the pulse is too quick; the strength and flesh waste; the skin is in a burning heat, without the least tendency to sweat; the thirst makes these patients drink immoderately, and of course they make water much more frequently than is common to them, and in much larger quantities, like hysterical persons. . . . The urine in a diabetic is said to have a honey-like sweetness; but, in my judgment, formed upon the most perfect cases of this distemper, it ought in most persons rather to be called insipid; in one joined with a fever, I found it sweetish.

Even more illustrative of Heberden's clinical portraiture is the account of angina pectoris first published in 1768.[8] Indeed, this account may be taken as a proper model for the natural history of disease. Abstracted in essential detail, it reads:

The seat of it, and sense of strangling and anxiety with which it is attended, may make it not improperly be called angina pectoris.

They who are afflicted with it, are seized while they are walking (more especially if it be up hill, and soon after eating) with a painful and most disagreeable sensation in the breast, which seems as if it would extinguish life, if it were to increase or continue; but the moment they stand still, all this uneasiness vanishes.

In all other respects, the patients are, at the beginning of this disorder, perfectly well, and in particular have no shortness of breath, from which it is totally different. The pain is sometimes situated in the upper part, sometimes in the middle, sometimes at the bottom of the os sterni, and often more inclined to the left than to the right side. It likewise very frequently extends from the breast to the middle of the left arm. The pulse is . . . not disturbed by this pain. . . . Males are most liable to that disease, especially such as have passed their fiftieth year.

After it has continued a year or more, it will not cease so instantaneously upon standing still; and it will come on not only when the persons are walking but when they are lying down, especially if they lie on their left side, and oblige them to rise up out of their beds. In some inveterate cases it has been brought on by the motion of a horse, or a carriage, and even by swallowing, coughing, going to stool, or speaking, or any disturbance of mind. . . .

Some have been seized while they were standing still or sitting; also upon first waking out of sleep; and the pain sometimes reaches to the right arm, as well as the left, and even down to the hands, but this is uncommon: in a very few instances the arm has at the same time been numbed and swelled. . . .

The termination of the angina pectoris is remarkable. For, if no accidents intervene, but the disease go on to its height, the patients all suddenly fall down, and perish almost immediately. Of which indeed their frequent faintnesses, and sensations as if all the powers of life were failing, afford no obscure intimation.

Infectious Diseases

Unfortunately such accuracy of clinical observation is the rare exception in modern medical writings. This deficiency becomes increasingly apparent in the welter of laboratory data, relevant and irrelevant, that so frequently clutters papers in the medical journals. The natural history of the infectious diseases has been reasonably well recorded. Particularly is this true where the etiological agent has been isolated. Contributing to the adequacy of the natural history of the acute infections has been their clear-cut definition and their self-limiting course in many instances. The knowledge of exposure and the routes and portals of entry of the etiological agents has been quite comprehensive. The ability to establish incubation periods, prodromes, symptoms and signs of the fastigium and the manner of defervescence to convalescence for the acute infectious diseases has lent great impetus to this effort. In most instances, the laboratory has afforded material support to the completion of the individual picture. Great hiatuses still exist in the knowledge of susceptibility and immunity. Actually, the advent of the antimicrobial agents, while a great beneficence to humanity, has delayed the attack on some unsolved problems in this area. In the first place, the opportunity to study the natural history of a given bacterial infection is limited by the almost universal administration of antimicrobial agents at the earliest moment. Not infrequently, the broad-spectrum antimicrobial agents have been given on suspicion before the etiology has been established. The vis medicatrix naturae is overlooked in the medical thought of many contemporary physicians. Certainly, Gairdner's admonition[9] is completely outmoded in modern medicine:

"There is one stipulation that I must make with those who desire to follow out this inquiry with the view of testing the normal mode of the crisis in typhus fever. It is, that *as many cases as possible should be left to their normal course, unaffected by either drugs or stimulants.*" Assuredly, the effectiveness of the antimicrobial agents in the treatment of lobar pneumonia, typhoid, and a host of other bacterial diseases seriously delimits any prospect of extending the knowledge of their natural history. A further deterrent to advances in this area has been the shifting emphasis in interest and study. This circumstance is doubly unfortunate in the unexplored fringes of this broad field.

Constitutional Disorders

The case of the constitutional disorders is much more involved. Many of the factors formerly attributed to heredity are now viewed as environmental and even infectious in origin. The area is wide open for a frontal attack. The degenerative and neoplastic diseases afford a fallow field for this approach. Mackenzie forsook a lucrative practice and an assured future in Harley Street to pursue this angle in St. Andrews, Scotland. He had two objects: "(1) understanding of the mechanism of symptoms, and (2) understanding of their prognostic significance."[5] In his biographer's phrase he urged his contemporaries "to forsake the study of death for that of life."[10] The way is not easy, but the future growth of clinical medicine is inextricably bound with a refinement and a discriminating use of the proved methods of clinical observation. The pathogenesis of atherosclerosis, for example, will be more clearly understood when all contributing factors in its initiation are brought into focus and their relative importance fixed. The familial occurrence of vascular degeneration is a commonplace observation, yet heredity has been discredited in some studies and dietary factors have been given increasing responsibility. The exact part of faulty cholesterol metabolism in the ultimate atherosclerotic process is still uncertain. The pendulum is apparently swinging toward a secondary relationship. In developing the natural history of this degenerative disorder, increasing attention must be devoted to the detailed history, with especial reference to the occurrence and the complications of past illnesses, social history, including habits and exposures, family history, and the evolution of the referable complaints. Since physicians have a conspicuous predisposition to atherosclerosis, they might render a conspicuous service by affording clinical autobiographies in this direction. Added to this approach would be the invaluable laboratory studies that anticipate and measure gross changes in pathological physiology. Billings[11] wrote, "Medicine today is applied science. If we utilize the knowledge of today in an attempt to cure and prevent disease, it must also be an experimental science . . . . Experimental medicine must be the means of removing the ignorance which still embraces so many of the maladies which afflict manhood."

Neoplasia arises from so many causes as to render a generic factor difficult of definition. Yet there may prove to be a single basic etiology with a number of variants responsible for the development of specific new growths. Painstaking studies of patients with neoplasms may add materially to our knowledge of their inception and course. Furthermore, especial attention to departures from the rule in apparent susceptibility and resistance to given tumors in certain strains may afford leading clues to the fundamental origin of neoplasia. While great progress has been made in this direction, the clinician is woefully deficient in the tools for the early recognition of a majority of visceral tumors. Surface or accessible neoplasms will receive early and appropriate attention in most instances, but carcinoma of the pancreas, for example, has usually reached an inoperable stage when surgery is proposed. Deep-seated upper abdominal pain radiating to the back, painless progressive jaundice, sudden diabetes mel-

litus in individuals past 45 years of age, and unexplained phlebothrombosis are late manifestations of carcinoma of the pancreas. Yet they may be the first symptoms or signs that bring the patient to the physician. Frequently, cachexia has already become manifest. In a few patients, vague upper abdominal discomfort, coupled with marked introspection and nervousness, has anticipated frank symptoms and signs of carcinoma of the pancreas by months in our experience. In carcinomatous involvement of the head of the pancreas, melena, occult or overt, may be a guidepost. In such instances, roentgenologic confirmation may be anticipated. The chemical studies directed toward the quantitation of the digestive ferments of the external secretion of the pancreas afford little support to the early diagnosis of carcinoma. Here, then, lies one of the unsolved mysteries of medicine whose solution may be expedited by an "exact Diary of the Disease." Its parallels are innumerable.

If Hippocrates [12] be forgiven his sententious vein, the following quotation affords an excellent argument for a profound knowledge of the natural history of disease:

> And he will manage the cure best who has foreseen what is to happen from the present state of matters. For it is impossible to make all the sick well; and this, indeed, would have been better than to be able to foretell what is going to happen; but since men die, some even before calling the physician, from the violence of the disease, and some die immediately after calling him, having lived, perhaps, only a day or a little longer, and before the physician could bring his art to counteract the disease; it therefore becomes necessary to know the nature of such affections, how far they are above the power of the constitution; and, moreover, if there be anything divine in the diseases, and to learn a foreknowledge of this also. Thus a man will be the more esteemed to be a good physician, for he will be better able to treat those aright who can be saved, from having long anticipated everything; and by seeing and announcing beforehand those who will live and those who will die, he will thus escape censure.

Obviously, prognosis is a vital element in the practice of medicine. Its cultivation and acquisition are avidly pursued by all clinicians worthy of the name. Recently, Bloomfield [13] wrote a cogent editorial on the subject, in which he evaluated the factors in deriving such conclusions. With experience, he stated, "the analytical process may become lightning fast and indeed may be largely carried on subconsciously. The young doctor, however, may well profit by deliberately taking into account the various factors in prognosis . . . and by making a conscious analysis of the situation in case of his patients. Such a running of mental scales will help develop later virtuosity." With incisive insight, Ryle [14] remarked, "Prognostic ability is born largely of pathology and patiently gathered clinical experience. It evolves even more slowly than diagnostic ability. Minute and careful clinical observation, a good visual memory, and that necessary inquisitiveness about the subsequent course of cases which is nowadays systematized in the follow-up inquiry may all be numbered among the handmaidens of prognosis."

Conclusions

In a word, there is no royal road to success in the prognosis of human disease. Feeble though the reed may appear when tested by strict scientific standards, the patient or the family may properly expect general information as to the probable course of a given illness from the physician. Fortified by extended experience and careful study of the problems presented by the patient, the true natural historian, supported by discriminating laboratory studies, will become increasingly proficient and accurate in assembling the evidence for the diagnosis and prognosis. Furthermore, with a sound basic knowledge of the natural history of disease, he will not fall into the uncritical habit of therapeutic sophistry, but, with a broad perspective, his therapy will have direction and his conclusions of its effectiveness will reflect measured judgment.

"Sit down before fact as a little child, be prepared to give up every preconceived notion, follow humbly wherever and to whatsoever abysses nature leads, or you shall learn nothing" (Huxley).

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Management of Hypertension

Pharmacology of the Useful Antihypertensive Drugs

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In the absence of more extensive knowledge concerning the etiology of essential and malignant hypertension, current attempts at their management with drugs necessarily consist of symptomatic therapy. Such therapy is directed largely toward lowering the elevated blood pressure, either for short periods of time and on isolated occasions when a hypertensive crisis is present or imminent or on a more continuous schedule with day-to-day medication. The principles upon which such symptomatic treatment are based are (1) that reduction of the elevated pressure may reduce symptoms and cardiac work and may prevent retinal and cerebral hemorrhages; (2) that it may prevent or retard progressive arteriolar injury and thus intensification of the disease process.

The purpose of this pharmacological discussion is not to evaluate the concept of using hypotensive agents in the therapy of hypertension or to assess the therapeutic value of the procedure. Rather it is to outline briefly the known or proposed pharmacological actions of the important antihypertensive drugs in current use. The actions responsible for the reduction in pressure may also produce important side-effects which restrict use, and some of the drugs produce additional side-effects because of pharmacological properties unrelated, or only indirectly related, to the antihypertensive action.

Limitations of time prevent detailed discussions of the innumerable investigations dealing with the pharmacology of antihypertensive drugs. These have been summarized in a number of reviews, which served as the major source of reference for this synopsis.*

A logical classification of drugs from a pharmacological standpoint is one based on site of action. In the case of some of the currently used antihypertensive agents this cannot be done without reservation. With these the reduction of blood pressure results from actions at more than one site, and in other cases opposing evidence and theory exist concerning the site of action involved, or of primary importance. Specific drugs are therefore omitted from the following classification but are discussed in the text where multiple sites of action, known or proposed, can be invoked when necessary.

1. Drugs which exert a depressant action on the central nervous system
2. Drugs which decrease sympathetic motor activity
   - (*a*) Adrenergic blocking agents
   - (*b*) Ganglionic blocking agents
   - (*c*) Centrally-acting inhibitors of sympathetic motor activity
   - (*d*) Drugs which increase afferent vascular reflexes
3. Drugs producing a direct relaxation of vascular smooth muscle
4. Drugs which act by unknown or multiple mechanisms

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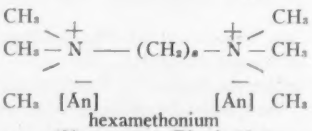
* References 1 and 2.

The contributing role of emotional and neurogenic factors in hypertension supplies a logical basis for the use of sedatives as adjuvants in therapy. Phenobarbital is still the principal drug used, along with psychotherapeutic measures such as rest and reassurance, by some physicians who are not convinced of the beneficial effects of drugs which lower blood pressure by relatively direct pharmacological mechanisms except in hypertensive crises. The prolonged duration of action of phenobarbital makes its administration in small sedative doses preferable over that of the shorter acting barbiturates. The hypotensive action of Rauwolfia serpentina and its alkaloids and of chlorpromazine is in all probability due partly to their tranquilizing, anxiety-dispelling action on the central nervous system.

Increased sympathetic vascular tone is believed by many to be a major contributing factor in the increased peripheral vascular resistance of hypertension. On this basis it is logical that drugs blocking the transmission of sympathetic vasoconstrictor impulses to effector cells in arterial and arteriolar walls should be regarded as potential antihypertensive agents.

On a theoretical basis, drugs blocking such transmission at the sympathetic nerve endings only would seem ideal and less prone to produce side-reactions due to other pharmacologic effects. Thus, the concept of adrenergic blockade was initially regarded with optimism. The drugs involved do not block sympathetic cardioaccelerator impulses to the heart. Piperoxan (Benodaine), Dibenamine (N,N-dibenzyl-β-chloroethylamine), phenoxybenzamine (Dibenzyline), azapetine (Ilidar), phentolamine (Regitine), and tolazoline (Priscoline) serve as examples of the class of drugs known as adrenergic blocking agents. They block the action of circulating epinephrine and *l*-arterenol more readily than sympathetic vasoconstrictor impulses, thus unmasking the vasodilating effect of the former on certain vascular beds. The latter fact makes them valuable in differentiating hypertension due to pheochromocytoma from essential hypertension. The larger doses which produce blockade at the endings of the sympathetic vasoconstrictor nerves unfortunately produce side-effects associated with this action and with actions on the central nervous system. Marked tachycardia and palpitation, severe postural hypotension, nasal congestion, nausea, vomiting, abdominal distress, weakness, and drowsiness severely limit the parenteral use of these agents in the treatment of hypertension. Oral treatment with Dibenzyline has led to variable results and disappointment.[1] For these reasons the adrenergic blocking agents have not gained wide use in the treatment of hypertension.

There are now available a considerable number of organic nitrogenous bases which block transmission of impulses from preganglionic nerve endings to the cells of postganglionic neurones in the autonomic ganglia, both sympathetic and parasympathetic. Production of the neurohumoral transmitter acetylcholine at the synapse is not decreased, but response of the postganglionic neurone to the acetylcholine produced is decreased or abolished. The blockade is not preceded by stimulation and does not extend to other sites of neurohumoral transmission (postganglionic autonomic endings and neuromuscular junction) in the usual doses. In the case of more recent compounds which produce more complete ganglionic blockade than the original agent, tetraethylammonium, the action of these drugs has been regarded by some as reversible, temporary, chemical sympathectomy, though complete block of all ganglia may not be obtained with the usual tolerated doses. The classical example of this group of agents is hexamethonium.†



hexamethonium
(Hexameton, Bistrium)

† References 1-3.

The ganglionic blocking agents produce vasodilatation and hypotension due to interruption of sympathetic vasoconstrictor impulses at sympathetic ganglia. Compensatory cardiac reflexes are also blocked. Total peripheral resistance is decreased. The vasopressor effects of circulating epinephrine and *l*-arterenol are not abolished, since the block is at the ganglion and may in fact be accentuated due to absence of reflex compensation caused by the blockade. A decrease in venous constrictor tone with venous pooling and decreased venous return also occur. Local vascular accommodation probably accounts for the fact that a marked and sustained decrease in flow does not occur in vital peripheral vascular beds (e. g., renal and cerebral) unless the hypotension is marked and unless pathologic vascular changes are advanced. Glomerular filtration rate, sodium excretion, and urine volume may be reduced considerably initially but tend to recover gradually, except for volume, despite maintainence of a reduced pressure, unless this is considerable.

Unfortunately, individual responses to parenteral administration of hexamethonium, pentamethonium, and the related compounds pentolinium (Ansolysen) and Pendiomide (N,N,N′,N′-3-pentamethyl-N, N′-diethyl-3-azapentylene-1,5-deammoniumdibromide), varies widely within the same patient and from patient to patient. Oral therapy is further complicated by the fact that these quaternary ammonium bases are poorly absorbed from the gastrointestinal tract, necessitating doses 10 to 20 times as great as those given parenterally. Variations in gastrointestinal motility and in the absorptive activity of the mucosa may change the degree of absorption and lead to decreased effectiveness or overdosage. The new unsymmetrical compound chlorisondamine (Ecolid) is claimed to have a longer duration of action than the methoniums, to be absorbed more readily, to have a more consistent action, and to produce fewer gastrointestinal side-effects.‡ The recently introduced secondary amine mecamylamine (Inversine), containing a tertiary rather than a quaternary nitrogen, is of great interest since it is completely absorbed from the gastrointestinal tract, thus eliminating one of the major disadvantages of other ganglionic blocking agents.§ Because of complete absorption the effective oral dose range of mecamylamine is much lower than that of the quaternary compounds, and it is hoped that the hypotensive action will be much more consistent and predictable.

Side-effects of the ganglionic blocking agents result from blockade of both sympathetic and parasympathetic pathways. The former results in postural hypotension and nasal congestion. The latter produces obstipation and ileus, impotence in males, dryness of the mouth, blurring of vision due to loss of accommodation, nausea, anorexia, and difficulty in micturition due to decreased bladder tone.

The fact that certain alkaloids of ergot can abolish the vasopressor effect of epinephrine and of sympatholytic stimulation in dogs under certain experimental conditions has been known for many years. The dihydrogenated alkaloids of the ergotoxine group (ergocryptine, ergocristine, and ergocornine) have been studied clinically as antihypertensive agents. Hydergine is a mixture of the three dihydrogenated alkaloids; dihydroergocornine alone has also been studied. Conclusions from laboratory studies, and to some extent from clinical observations, indicate that these compounds do produce hypotension, but on a different basis than that of peripheral adrenergic and sympathetic blockade. Their major action appears to be one of central depression of sympathetic vasomotor tone.[2] As in the case of the veratrum alkaloids, they also possess some ability to depress vasomotor reflexes and to produce central vagal stimulation. The dihydrogenated ergot alkaloids are much less effective orally than parenterally, and tolerance to their hypotensive action is claimed to develop quite rapidly. Side-

‡ References 4 and 5.

§ References 6 and 7.

effects include postural hypotension, tachycardia, nasal congestion, lethargy, flushing, sweating, and headache. They are not among the most important or frequently used antihypertensive drugs at the present time.

The veratrum alkaloids have received extensive attention as antihypertensive agents, first as relatively crude mixtures of the plant alkaloids and recently as more purified fractions. The alkaloids are of two types: tertiary amine esters, such as protoveratrines A and B and veratrine, and secondary amines, such as veratramine, which occur naturally in the form of glycosides.‖ Among the preparations available for therapeutic use are alkavervir (Veriloid), Vergitryl (ester alkaloid fraction of veratrum viride), protoveratrines A and B (Veralba), protoveratrine A and B maleates (Provell Maleate), and cryptenamine (Unitensen).

The site of action of veratrum alkaloids has been studied exhaustively by Krayer and his associates.[8] The hypotensive action is produced by cardiodeceleration and peripheral vasodilatation resulting from an increase in the number of afferent discharges in certain reflex circulatory pathways. Various investigators do not agree on the origin of these reflexes or on the efferent pathways involved, possibly because different alkaloids differ quantitatively and qualitatively in their actions. The receptors from which the afferent pathways of the reflex arise are reported to be in the left ventricle, the lungs, the carotid sinus region, and possibly the brain.[1] The efferent arm of the cardiodecelerating reflex is vagal, since it is abolished by atropine or vagotomy in the case of at least some of the alkaloids. The fact that cardiodeceleration produced by other veratrum alkaloids is not thus abolished may indicate a direct effect on the cardiac pacemaker. Inhibition of sympathetic pathways constitutes at least a part of the efferent arm of the vasodilating reflex. Other pharmacological effects of the veratrum alkaloids on the cardiovascular system have been described but are important only at doses greater than those used clinically, e. g., cardioacceleration, vasopressor effects, and a direct increase in cardiac contractile force.[1]

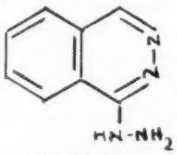
The veratrum alkaloids have a prominent (reflex?) emetic action which often occurs at the same doses as does the hypotensive action, suggesting a common reflex origin for the two effects. If true, the efferent pathways must be different, since atropine, which antagonizes the cardiodeceleration, does not affect the emesis. Receptors in the nodose ganglion have also been postulated as the site at which the emetic and some of the hypotensive reflex effects originate.[3] Recent studies with newer, more highly purified and separated veratrum fractions, such as cryptenamine, have raised some hopes that the emetic and cardiovascular actions can be dissociated to some extent.

The decrease in total peripheral resistance following administration of veratrum alkaloids does not result in marked hyperemia, autonomous mechanisms for readjustment of regional circulation being relatively intact. Renal blood flow is not markedly affected unless moderately severe hypotension occurs or vascular disease is advanced. With moderate therapy an initial fall is frequently followed by a gradual return toward normal. Since reflex compensatory pathways for circulatory adjustment are not impaired by veratrum alkaloids, and possibly because they do not influence venous tone, postural hypotension is not as outstanding a side-effect as with the ganglionic blocking agents. Severe hypotension even at rest does occur at times due to unexplained fluctuations in the susceptibility of individual patients to the drugs. Nausea and vomiting are the commonest side-effects and are more frequently encountered with oral than with parenteral therapy. Other side-actions are precordial distress, sensations of warmth and paresthesias in the extremities, and cardiac irregularities.

Hydralazine (1-hydrazinophthalazine, Apresoline) is difficult to classify be-

‖ References 8 and 9.

cause of a persistent lack of agreement and of conclusive evidence concerning its site of action. Its effects differ from those of other agents in that its hypotensive action is accompanied by an increase in renal blood flow and a marked increase in cardiac output.[10] In dogs, the increased cardiac output and a marked tachycardia can occur without attendant vasodepressor action and are abolished by sympathectomy and ganglionic blockade.¶ Doses which produce an increase in renal blood flow do so even after ganglionic blockade.



Hydralazine
(Apresoline)

It has been proposed by various investigators that hydralazine acts by producing a central inhibition of vasomotor reflexes, by a direct relaxing effect on vascular smooth muscle, by antagonizing the action of humoral vasopressor substances such as serotonin, angiotonin, epinephrine, pherentasin, or central vasoconstrictor substance, or by complexing certain metallic ions.# Evidence that any of these explain the antihypertensive action is inconclusive or conflicting. That it does not act by ganglionic blockade is established, and its weak activity in antagonizing epinephrine and *l*-arterenol is not accepted by many investigators as a basis for mechanism of action. A mechanism involving histamine release has been postulated but is inadequately supported even by evidence that the drug can inhibit histaminase. Conflicting reports and inadequate evidence exist concerning its effect on flow in perfused limbs. More studies along these lines and lines similar to those used in elucidating the mechanism of action of veratrum on cardiovascular reflexes would be helpful. Splanchnic as well as renal blood flow is increased by hydralazine. Cerebral blood flow is maintained but not increased despite the suggestion that the side-reaction of headache is based on cerebral hyperemia.

Hydralazine has been used both orally and parenterally. Its analytical recovery from urine is low in both cases and thus cannot be explained on the basis that the drug is poorly absorbed from the gastrointestinal tract.[14] In view of the proposed central site of action of hydralazine, studies concerning its distribution in the nervous system of animals would be of interest, as would studies of its effect on the concentration of serotonin in the central nervous system (*vide infra*).

Unfortunately side-effects impose limitations also on the use of hydralazine. Headache is frequently encountered. Nausea and vomiting also occur. Palpitation and nervousness are related to the cardiac effects of the drug and the latter possibly also to a central nervous action. Urticarial reactions are ascribed to "histamine-liberating" properties of the drug. Postural hypotension is a serious complication only with intensive therapy. Prolonged intensive therapy has produced a syndrome simulating lupus erythematosus. Because of its tendencies to sustain or increase renal blood flow and to produce side-effects when used alone, its combination with other agents has been recommended and studied clinically.

Rauwolfia serpentina and its purified constituents, such as reserpine and rescinnamine, are the most recent addition to the list of antihypertensive drugs studied in this country. They have been shown to lower blood pressure and to produce bradycardia in experimental animals and in some hypertensive patients following oral and parenteral administration.[15] The tranquilizing effect of these drugs may in itself be responsible for the relief of subjective symptoms in patients with hypertension and may contribute to the decline in blood pressure, but other factors are probably involved. The hypothalamus, postulated as the site of the tranquilizing and hypothermic ac-

¶ References 11 and 12.
# References 1 and 13.

tion of rauwolfia alkaloids, is believed also to be the site of their hypotensive and bradycardiac action. As pointed out by Plummer and co-workers,[15] some responses of animals to reserpine (e. g., relaxation of the nictitating membrane) suggest a decrease in sympathetic predominance, while other responses, such as miosis, bradycardia, and increased gastrointestinal activity, suggest an increase in parasympathetic predominance. The hypotensive action does not occur in spinal animals, and atropine partially inhibits the bradycardia effect.[1] Reserpine has been shown to prevent or diminish the rise in blood pressure produced by stimulation of the central end of the vagus and sciatic nerves and by carotid occlusion.[16] It has not been possible to demonstrate an adrenergic or ganglionic blocking action or a direct vasodilating action following intra-arterial injection.[17] Evidence such as this points to a central, rather than a peripheral, site of action.

A latent period and gradual onset of the hypotensive and bradycardic action of rauwolfia alkaloids has been reported.[18] This may be due merely to time required for a cumulative effect, since sufficiently large doses can produce more rapid effects. It has recently been shown that the hypotensive action of reserpine in rabbits following a single injection lasts several days and long after reserpine has disappeared from the brain, the hypotension being more closely related temporally to the depletion and regeneration of brain serotonin.[19] The investigators suggest that the action of reserpine may be mediated through serotonin, which may have a role in the normal regulation of blood pressure. Further studies along these lines will be of great interest, since they may shed further light on the etiology of hypertension and the possible role of brain serotonin as a controlling humoral mediator of cardiovascular hemostasis.

Reserpine is regarded by many as a "mild" antihypertensive agent. Side-effects include nasal congestion, increased gastrointestinal activity, lethargy, depression, and decreased libido in male patients. Excessive doses may produce nightmares, severe depression and anxiety, and a reversible Parkinsonian syndrome. It is noteworthy that postural hypotension is not a complicating factor with the usual therapeutic doses.

Summary and Conclusions

Rauwolfia alkaloids, veratrum, ganglionic blocking agents, and hydralazine are the principal antihypertensive drugs in current use. These drugs differ in the mechanism of action, and all display undesirable side-effects accruing from the same pharmacological properties which produce hypotension or from additional pharmacological actions. The sites of action of rauwolfia alkaloids, and especially of hydralazine, require further elucidation. Additional knowledge concerning these sites of action may increase understanding of the complex etiological factors underlying the symptom-complex of hypertensive cardiovascular disease.

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Intractable, Severe Hypertensive Disease

Observations on Resistance to Treatment with Current Drugs, Denervation of the Carotid Sinuses, Hypertensive Encephalopathy, and Other Complications

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Most current reports on antipressor drugs concern their effectiveness in groups of patients and give little consideration to cases in which drugs have been ineffective. Rather, the proportions that respond fairly are listed and some exemplary responses may be summarized.

The present report contrasts with this custom. It deals primarily with one patient whose severe hypertensive disease was not controlled by available drugs. Relevant observations made in other patients are noted. The data bear on the effects and complications of antihypertensive drugs and on effects of carotid sinus denervation; they are concerned also with the nature of hypertensive encephalopathy and the mechanism of hexamethonium resistance and, in brief, with unusual renal and metabolic symptoms and signs noted in this patient.

Report of a Case

The patient was found to have high blood pressure at a physical examination in 1947. When first seen at the Cleveland Clinic in November, 1951, which was taken as the 48th month of her disease, she was an attractive, cheerful Negro woman of 28, who had no other symptoms than some recent frontal headaches. She was employed as a nurse's aide in the hospital.

Her mother had died of a stroke when she was about 35 years of age.

Physical examination disclosed hypertension (220/140 mm. Hg, casual reading) with fundal arteriolar constriction (rated 2+) and sclerosis (1+).

Urinary concentrating power and urea clearance were within normal limits. She had some hematuria (5,200,000 red cells in 12 hours' urine) but no proteinuria. The electrocardiogram showed "myocardial changes," rated as 2+; heart size was increased to 125% of normal by the Ungerleider-Clark scale. These observations and the subsequent course of her illness are summarized graphically in the Figure.

Hydralazine.—This was begun in the 55th month, after repeated observations confirmed the presence of severe increases of casual blood pressure. It was given in doses of 500-700 mg. daily for five months (Figure, Nos. 1-2) but with little effect on casual pressures. She was admitted to hospital (No. 2) because of headache and vomiting. The weekly averages of twice-daily pressures were high, and failure of control of hypertensive disease was shown by the onset of retinal hemorrhages, exudates, and papilledema.

An area of painful induration was present in the right calf; the pathological diagnosis from a muscle biopsy in this area was periarteritis nodosa. No evidence of generalized polyarteritis was demonstrated at this time or during her subsequent course. The lesion subsided when hydralazine was withdrawn and did not recur when it was given again.

Hydralazine-Hexamethonium.—She was placed on hexamethonium and hydralazine therapy (Figure, Nos. 2-3). Averages of supine blood pressure decreased, and retinopathy cleared promptly. She was discharged from hospital, taking this combination of drugs, measuring pressures in the sitting position at home, and reporting their averages. During the next two months (61 and 62) these ranged about 190/120; she complained of postural hypotension. She became gradually depressed, reported somewhat irregularly as an outpatient, and, although her records indicated still lower pressures (160-180/100-110)in months 63 and 64, office pressures, sitting and standing, were high; there was no orthostatic hypotension, and retinopathy recurred. We had the impression that, concerned by her difficulties and fears, she "selected" low pressures for her records. Control, in

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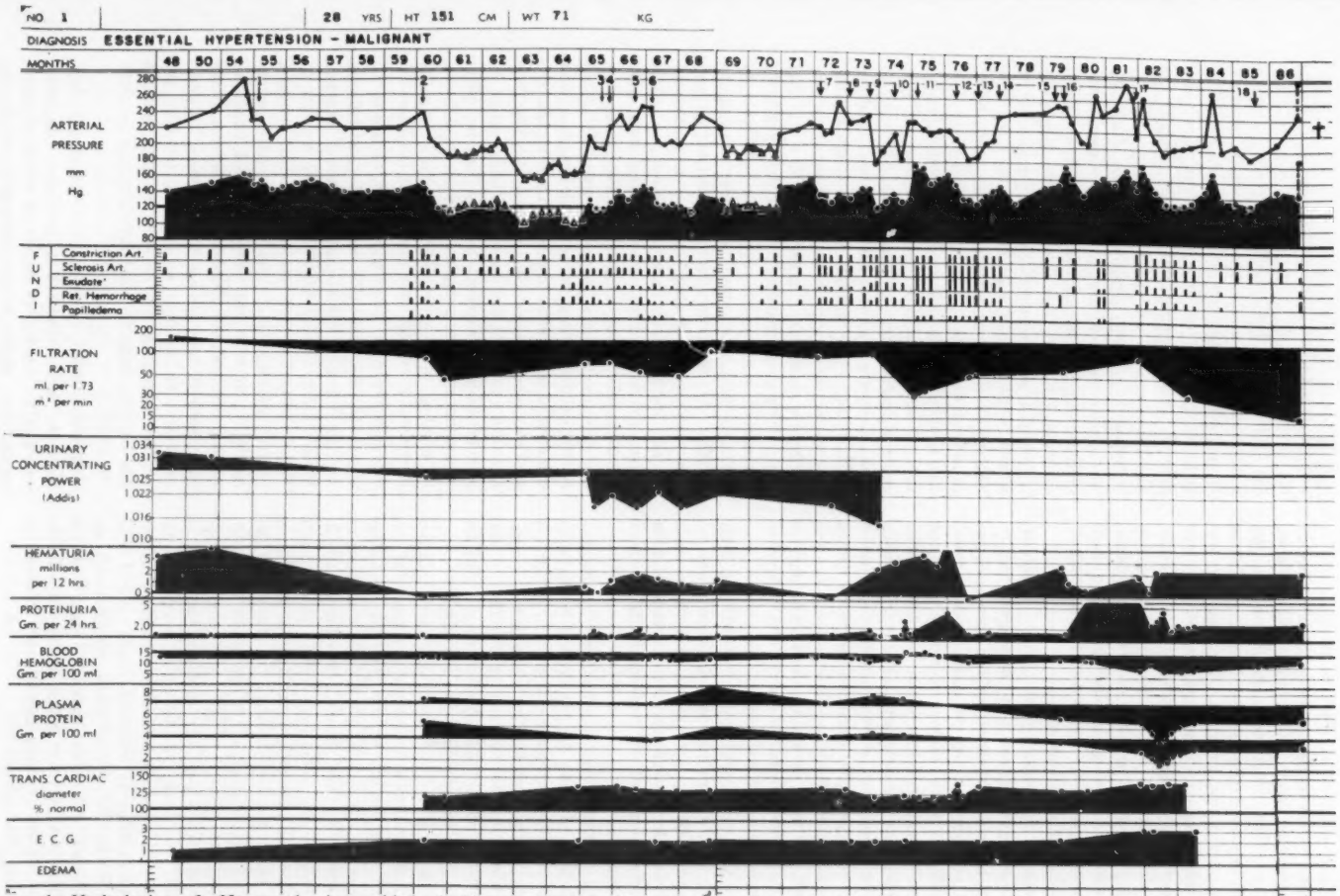
NO 1
28 YRS
HT 151 CM
WT 71 KG
DIAGNOSIS ESSENTIAL HYPERTENSION - MALIGNANT
MONTHS
48 50 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80 81 82 83 84 85 86
ARTERIAL PRESSURE mm Hg
280 260 240 220 200 180 160 140 120 100 80
FUNDI
Constriction Art.
Sclerosis Art.
Exudate
Ret. Hemorrhage
Papilledema
FILTRATION RATE ml. per 1.73 m² per min
200 100 50 30 20 15 10
URINARY CONCENTRATING POWER (Addis)
1.034 1.031 1.025 1.022 1.016 1.010
HEMATURIA millions per 12 hrs.
5 2 1 0.5
PROTEINURIA Gm. per 24 hrs.
5 2.0
BLOOD HEMOGLOBIN Gm. per 100 ml
15 10 5
PLASMA PROTEIN Gm. per 100 ml
8 7 6 5 4 3 2
TRANS CARDIAC diameter % normal
150 125 100
E. C. G.
3 2 1
EDEMA

1. Hydralazine. 2. Hexamethonium added. 3. Hexamethonium discontinued. 4-5. Iproniazid, subsequently isoniazid. 5. Encephalopathy (first attack), intravenous nitroprusside. 6. Hexamethonium and hydralazine. 7. Hydralazine discontinued. Bouts of encephalopathy. 8. Section of right ninth cranial nerve. 9. Grand mal type of encephalopathy. 10. Section of left ninth cranial nerve. 11. Pulmonary disease (hexamethonium ?). 12. Increased responsiveness to hexamethonium, attacks of left ventricular failure. 13. Low-sodium diet. 14. Discharge from hospital: sodium azide added to hexamethonium. 15. Hexamethonium discontinued. 16. Sodium azide discontinued. Pentolinium, intramuscular. 17. Nephrotic episode. 18. Reserpine added. Terminal episode in 86th month.

any case, was irregular and inadequate and she was readmitted, again with nausea and headache. She had slight proteinuria and hematuria, decreased urinary concentrating power, and some further cardiac enlargement. The regimen was continued for another three weeks, which confirmed its failure to control blood pressure levels, so that it was discontinued (Figure, No. 3). During this time an intravenous test dose of 174 mg. of hexamethonium had no effect on blood pressure (measured at 30 degrees tilt) and caused only a moderate (170/110) fall on standing.

Iproniazid (*Marsilid*)—This drug (1-isonicotinyl-2-isopropylhydrazine) had been given empirically to patients who developed the rheumatic and febrile syndrome during treatment with hydralazine.[3] One of these showed reduction of supine pressure averages which persisted over five months, with subjective improvement. Of the 12 patients given the drug, most showed orthostatic hypotension only; in one, this persisted for more than a year and was not disabling; in some others it was transient, and some showed no effect on blood pressure at all. Several gained weight and manifested a euphoric sense of well-being.

Iproniazid was given in doses of 400 mg. daily (Figure, No. 4) for two weeks, when it was replaced with 600 mg. daily of isoniazid (isonicotinic acid hydrazide), given over three weeks. Neither drug affected supine or standing levels of blood pressure.

Encephalopathy; Hexamethonium Resistance.—It was then (Figure, No. 5) several weeks since she had received hexamethonium. The possibility that she might have lost her resistance to its effects was tested by intravenous injection of 100 mg. At the end of the injection supine pressure was 230/150 and standing pressure 170/106

She woke at 1 a.m. on the day after this test with a severe headache. Blood pressure was unchanged from the day before (250/152) and pulse rate was 75. By 5 a.m. she became comatose; in the interval she had shown restlessness, drowsiness, nausea, and vomiting. Sodium nitroprusside was given intravenously over eight hours, during which blood pressure decreased to about 180/100; consciousness returned at the end of the first hour, and she was relieved of all but a slight frontal headache. At 6 p.m. her pressure had risen to 240/160; she again complained of severe frontal headache and showed the same syndrome as before, progressing to unconsciousness. Spinal fluid pressure was 170 mm. of water. Nitroprusside infusion again maintained systolic pressure at 140 mm. Hg over several hours, during which she rapidly regained consciousness and comparative well-being.

Hexamethonium was then given intravenously. The preinjection supine pressure was 254/172; after injection of 100 mg., pressure fell to 210/150, but rose to 250/150 in 20 minutes. On the next day, 200 mg. of hexamethonium given intravenously had only a slight effect on supine pressure (initial 270/160, minimum after injection 200/140), and, four days later, 500 mg. intravenously decreased pressure transiently from 260/154 to 210/146.

Although evidently resistant to the drug, she was placed on a regimen of intramuscular hexamethonium, 600-800 mg. daily, and hydralazine (Figure, No. 6). She showed some orthostatic hypotension and improved during the next three weeks, with remission of retinopathy; she was discharged for home and outpatient care. Blood pressures fluctuated greatly, ranging from 260-136/170-90, and she was readmitted briefly (69th month) because of retrosternal pain, which subsided without clear-cut diagnosis. Averages of home pressures indicated fair control at about 190/120, but office pressures were much higher, and retinopathy recurred. She was again admitted to hospital (Figure, No. 7). At that time 200 mg. of hexamethonium intravenously decreased supine pressure from 265/165 to 188/138, and the standing pressure fell to 118/84. Hydralazine was discontinued, and she was given reserpine orally as a supplement to the intramuscular hexamethonium. A week later, severe headache recurred and was only partially relieved by intravenous thiocyanate (1.0 gm. of the sodium salt[8]. Pressure was 246/162 and fell to 190/106 during nitroprusside infusion, with complete relief, until headache recurred on the next day when pressure had risen to 226/130. She was then given 3γ per kilogram of body weight of protoveratrine intravenously. This had no effect on supine pressure, provoked a moderate decrease in standing pressure to 170/110, a drop in pulse rate from 71 to 60, and tingling in the pharynx.

Hexamethonium (600 mg. daily, intramuscularly) and reserpine (2.5 mg. daily, orally) did not control her blood pressure, which reached levels of 270/140 and 300/160, with pulse rate of 44 and apathetic drowsiness as evidence of reserpine action. She developed repeated bouts of encephalopathy, each with the progression of headache, nausea, restlessness, drowsiness, and coma, and each controlled by giving nitroprusside intravenously for 12-24 hours in amounts (80-160γ per minute) which brought diastolic pressure to about 100 mg. Hg, with increases in pulse rate to about 70.

Hexamethonium Resistance; Spinal Anesthesia.—She was considered to be almost completely resistant to the supine depressor effect of hexamethonium, although she remained moderately responsive to its effects on standing pressure. This resistance persisted through her terminal episode

(described below), when it was shown that high spinal anesthesia to T 2 also had no depressor effect on her supine blood pressure.

Similar observations were made in others. One man of 36 with advanced malignant hypertension and uremia who had been taking inadequate doses of hydralazine and hexamethonium was admitted in encephalopathy with headache, restlessness, and vomiting. Hexamethonium intravenously in two widely spaced doses of 100 and 200 mg. had no effect on the levels of supine blood pressure, while nitroprusside, 90γ per minute, promptly brought the pressure to 140/100. Extradural anesthesia to T 2 decreased supine pressure from 220/160 to 180/130 (130/110, sitting). Another, a woman of 46 who was only slightly azotemic and who had shown resistance to pentolinium, responded to spinal anesthesia to T 2 with a slight rise in supine pressure. Another nonuremic patient, a man of 44, had no supine depressor effect from 40 mg. of hexamethonium intravenously and, six days after his last dose of hexamethonium, showed no fall of supine pressure during spinal anesthesia to T 2. The last of this group, a Negro woman of 28 with severe malignant hypertension and uremia, had shown increasing resistance in hospital to ganglion blockers, viz., pentolinium, Ecolid (4,5,6,7-tetrachloro-2[2-dimethylaminoethyl]isoindoline dimethochloride), and mecamylamine (Inversine). When readmitted with a pressure of 300/200, she responded to 13 mg. of Ecolid intravenously with a transient fall to 260/180, (supine) 190/130 (standing). Spinal anesthesia to T 1 had no effect on supine pressure and, as in other resistant patients, nitroprusside intravenously was strongly depressant.

Thus the patient being chiefly considered, in common with four other patients who were resistant to the supine depressor effects of ganglion blockers, was also resistant to the supine depressor effect of high spinal anesthesia.

Section of Right Ninth Cranial Nerve.—The nerves of the carotid sinus run intracranially in the ninth cranial nerves and accessible to the neurosurgeon for section in this part of their course.

Animal experiments indicated that section of these nerves increased sensitivity to vasodepressor drugs, such as hydralazine and hexamethonium.[4] This procedure was recommended to the patient with the hope of restoring her responsiveness to drugs and with due regard to her ominous prognosis.

The right nerve was cut (Figure, No. 8) by Dr. W. J. Gardner in the 73d month. The brain was not edematous. The postoperative course was stormy; nitroprusside infusions maintained pressure at about 160/100, but when these were discontinued, pressure rose to about 290/170, and she fell into restless coma. This sequence was repeated several times. Hexamethonium in repeated doses of 200 mg. every four hours intramuscularly had no effect on pressure. At the end of 36 hours nitroprusside infusion was stopped because of inflammation at the site of infusion, and she was given reserpine (8 mg. daily, orally,) and, intramuscularly, chlorpromazine (150 mg. every four hours) and protoveratrine (150γ every four hours). This combination elicited only vomiting. Nevertheless, reserpine was continued; oral was substituted for intramuscular chlorpromazine, and oral (0.75 mg. every six hours) for intramuscular protoveratrine.

Chlorpromazine and Protoveratrine.—In animals, chlorpromazine does not counter the veratum emesis as it does that due to other agents, such as apomorphine. This was verified in our patient, as noted above, and in six other patients. These were treated with protoveratrine or with alkavervir (Veriloid) to the point of nausea and then maintained at this or a slightly lower dosage while also being given chlorpromazine. The observations, reported elsewhere[5] showed only one patient with some apparent protection against the emetic action of the veratrum drugs.

Hypertensive Encephalopathy with Grand Mal.—The patient went home for Christmas. Two days later she awoke with headache. An hour after, a series of grand mal attacks began, which recurred almost hourly until she was readmitted that afternoon (Figure, No. 9). At this time she was comatose; diastolic pressure was 140 mm. Hg and cerebrospinal fluid pressure 155 mm. of water. The provisional diagnosis was encephalopathy, although blood pressure was not as high as it had been in her previous attacks. She was given nitroprusside intravenously (200γ per minute); failure to regain consciousness after several hours at a blood pressure of 120/70 confirmed the suspicion that this was not same as the encephalopathy she had had before. However, late that evening, her mind cleared.

Section of Left Ninth Cranial Nerve.—This was accomplished at the end of three weeks' observation (Figure, No. 10). The immediate postoperative course was less stormy than before, blood pressure being smoothly controlled by nitroprusside infusion at levels of about 150/100 for 24 hours, after which she was given intramuscular hydralazine and hexamethonium. On the 10th postoperative day, diastolic pressure rose to 168; she complained of blindness, had a grand mal attack and became unconscious, with arterial pressure 200/145. Over the next 36 hours she was given a total of 700 mg. of hexamethonium intravenously. Diastolic pressures decreased to about 100 mm. Hg. However, she had developed fever (101 F) and tachypnea (60 per minute), cough, and rales over the left lung. Roentgenograms showed increased left hilar markings. She also had a

clonic seizure and became unconscious and areflexic, with a fall of arterial pressures of 132/98, rising, two hours later to 170/100. An electroencephalogram showed diffuse "organic" changes; she was given diphenylhydantoin (Dilantin), 0.2 and 0.3 gm. daily, but a week later, with arterial pressures rising to levels of 240/190, another similar seizure developed. It was considered that, besides having cerebral lesions due to hypertensive disease, she had again become resistant to the depressor effects of hexamethonium and hydralazine; the chest roentgenograms were indicative of diffuse interstitial pneumonitis atributable to hexamethonium. Accordingly, hydralazine and hexamethonium were withdrawn, and diphenylhydantoin continued (Figure, No. 11).

The pulmonary distress promptly subsided. Seizures recurred with coma; at the onset of one of these blood pressure level was 240/170 and spinal fluid pressure 100 mm. of water. Diphenylhydantoin was increased to 0.4 gm. daily.

Electrolyte Disturbance; Hypercorticoidism(?).—During the 75th month it was observed that her face seemed rounder and that she had facial and pectoral acne and hirsutism. Serum analyses (CO_2 content 32.8, Cl 90, and K 3.8 mEq. per liter) suggested that she might have a potassium deficit, so potassium supplements were given in doses of 60-90 mEq daily over the course of four weeks, but without effect on serum electrolyte concentrations. During this time, glucose tolerance was found normal, urinary 17-ketosteroids a high normal (15 mg. daily), and 17 hydroxycorticosteroids (Porter-Silber) normal (3.2 mg. daily). The urine at this time was nearly neutral (pH 6.5 to 7.0). The condition persisted for about six months, after which it slowly subsided.

She also again became responsive to hexamethonium, so that an injection of 136 mg. decreased pressure to 100/70 from a level of 232/172 (Figure, No. 12). This hypotension was associated with an apathetic negativism and with oliguria, both of which persisted for two days. Subsequently she showed sharp weight gains and had a bout of left ventricular failure. Proteinuria and hematuria had increased, and it was believed that her disease was rapidly advancing. She was digitalized and placed on sodium restriction. An intramuscular test dose of 25 mg. of hexamethonium decreased pressure from 220/160 to 188/138 (supine) and 120/100 (standing) five hours later. Treatment with intramuscular hexamethonium was resumed; she demonstrated rapidly increasing tolerance.

She was released from hospital a month later. In addition to hexamethonium intramuscularly she was given sodium azide (Figure, No. 14) orally. This, in 1 mg. sublingual doses, elicited palpitation and was transiently depressant, but it had no effect on averages of supine pressure; the experience in 14 other patients was similar. Hexamethonium was discontinued (Figure, No. 15) and later sodium azide (No. 16). She was given pentolinium (Figure, No. 17) intramuscularly; the dosage was increased to 16.5 mg. every eight hours, at which time supine blood pressure average was 205/134 and standing average 185/123; the addition of reserpine (0.5 daily, orally) had no further effect. During this time she had been shown to be insensitive to protoveratrine; 130γ intravenously at a rate of 10γ per minute did not affect blood pressure, nor did it change pulse from a preinfusion rate of 100 per minute. She had another grand mal attack with precedent blindness, after which diphenylhydantoin dosage was increased to 0.5 gm. daily.

Nephrotic Episode.—She gained about 20 lb. in weight during the 82d month and developed pitting edema. Blood urea was 57 and serum creatinine 1.68 mg. per 100 ml., serum albumin had decreased to 2.9 gm. per 100 ml., and urine protein had increased to about 8 gm. daily. She lost 13 lb. in weight when given a potassium-ammonium cycle carboxylic resin, ammonium chloride, and mercurials; she was unable to maintain sodium restriction at home, and was readmitted at the end of the month. At this time serum albumin was only 1.9 gm. per 100 ml., and proteinuria was about 10 gm. daily. She had gingival hypertrophy and was edematous. She was given acetazolamide (Diamox) in intermittent courses, a diet containing about 0.5 gm. sodium daily and, at the end of the 83d month had lost 30 lb. in weight (10 lb. of this in three days) and was free of edema. During this time proteinuria decreased and serum albumin rose to 2.6 gm. per 100 ml. A urinary 17-hydroxycorticoid analysis indicated a normal output of 2.7 mg. daily.

Terminal Episode.—She was readmitted late in the 86th month because of nausea, vomiting, and severe headache of three days' duration. Blood urea was now 105 and serum creatinine 4 mg. per 100 ml.; urea clearance was 15% of normal. Pentolinium intravenously in amounts up to 6 mg. was without effect on blood pressure. Confusion and restlessness were evident and did not respond, but increased during nitroprusside infusion, which brought blood pressure to 180/110. Trimethaphan camphorsulfonate (Arfonad), a thiophanium derivative, did not decrease blood pressure in a dose of 1 mg. per kilogram, and spinal anesthesia to T 2 was equally ineffective; nitroprusside was still depressant. Three days after admission blood urea had risen to 210 mg. per 100 ml. and serum creatinine to 16.6. Blood pressure during nitroprusside infusion was 180/90 mm. Hg and cerebrospinal fluid pressure 45 mm. of water. When nitroprusside was discontinued

on the following day, the blood pressure rose to 300/190 mm. Hg, and she had a convulsion. She died on the following day, without regaining consciousness.

Pathological Report (Dr. L. J. McCormack.—The heart weighed 625 gm. and showed no gross evidences of coronary atherosclerosis or myocardial infarction. The aorta showed only a few small atheromatous plaques. The liver (1900 gm.) and spleen (220 gm.) showed congestion and edema, and, microscopically, slight focal interstitital fibrosis. The ninth cranial nerves were found to have been severed intracranially, with dural adhesions in the posterior fossa at the operative sites. The right superior temporal gyrus showed a soft, shrunken, yellow depression, and a like area was found on the inferior surface of the right frontal lobe. Multiple microscopic sections of the brain failed to demonstrate recognizable abnormalities, and the cerebral vessels were not grossly abnormal.

The pancreatic arterioles were severely sclerotic. The renal arteries showed diffuse "onion-peel" lamination, and the arterioles necrosis, with corresponding widespread glomerular hyalinization, focal necrosis, tubular atrophy, and dilatation with cast formation; these lesions were diagnosed as those of severe, active, malignant nephrosclerosis. The adrenals (10 gm. each) were grossly hyperelastic but microscopically not remarkable.

Serum Proteins and Lipoproteins.—Serum proteins were followed through the latter course of the disease by Dr. Lena Lewis, using the Tiselius-Longsworth method, and lipoproteins by Gofman's ultracentrifugal method, as modified by Lewis, Green, and Page.[6] Serum total cholesterol was measured by the method of Abell, Levy, Brodie, and Kendall.[7] These data are listed in Tables 1A and 1B.

The first three observations were within normal limits. During the nephrotic episode (82d month) albumin and γ-globulin decreased, α-globulin and β-globulin showed increases in relative concentration. These changes tended subsequently to be restored toward normal. No well-defined abnormalities were demonstrated in the lipoprotein patterns except that β-lipoproteins (—S25-40, 40-70) tended to be slightly increased throughout the course. Total cholesterol was within normal limits at all times.

Cardiovascular Reactivity.—The method of study was essentially that used by Page and Taylor[8] in dogs. The tests were performed by Dr. Jean Mignault. A catheter was placed in the basilic vien for injection of test substances,

TABLE 1A.—*Serum Proteins (Tiselius) During the Course of Diseases*

Month	Total Protein	Albumin		Globulin					
				Alpha		Beta		Gamma	
		gm.	%	gm.	%	gm.	%	gm.	%
66	7.00	3.90	55.6	0.60	8.6	1.07	15.3	1.43	20.5
68	----	----	----	----	----	----	----	----	----
72	7.00	4.22	60.3	0.48	6.9	0.91	13.0	1.39	19.8
74	7.61	4.41	57.6	0.59	7.8	1.05	13.8	1.56	20.5
79	5.93	3.81	64.3	0.27	4.5	0.89	15.0	0.96	16.2
81	5.60	2.92	52.3	0.82	14.6	0.95	16.9	0.91	16.2
82	3.85	1.91	49.7	0.64	16.6	0.98	25.5	0.32	8.2
82	4.13	1.95	47.0	0.83	20.2	0.81	19.6	0.54	13.2
82	4.97	2.59	54.1	0.60	12.5	0.95	19.8	0.65	13.6
83	5.17	2.83	58.4	0.71	13.7	0.91	17.5	0.72	14.0
83	5.83	3.11	53.4	0.61	10.4	1.04	17.8	1.07	18.4
86	5.79	3.35	57.7	0.57	9.9	0.82	14.1	1.05	18.3
Control mean females 18-34	7.44	4.74	63.4	0.54	7.2	1.11	15.2	1.04	14.1

TABLE 1B.—*Serum Lipoprotein and Cholesterol Concentrations*

Month	40-70	40-70	25-40	20-25	1-10	Total Cholesterol.
66	19	16	106	19	282	153
68	..	7	166	19	188	173
72	..	14	164	19	270	185
74	..	38	118	19	258	192
79	28	47	343	7	199	232
81	..	19	212	12	118	236
82	12	83	258	9	164	187
82	12	28	212	12	166	n.d.
82	12	42	218	38	148	227
83	14	14	166	33	306	226
83	16	33	228	45	329	249
86	14	26	141	16	294	223
Control mean females 18-34	22	18	200	12	210	216

and arterial pressure was electrically recorded from the brachial artery. The test substances used were nitroprusside, arterenol, (norepinephrine), serotonin, and tetraethylammonium chloride (TEAC).)

Table 2 demonstrates the progressive rise of diastolic pressure in the control periods of the tests. Nitroprusside was depressant in all tests, possibly somewhat less in the last. The last two tests also show diminished pressor responsiveness to arterenol; in these also, serotonin, which had been pressant, became depressant. Responses to TEAC were pressant, indicating partial ganglionic blockade[9] or slightly depressant, the significant finding here was that TEAC was not, as it is in experimental neurogenic hypertension, strongly depressant. Responses to angiotonin, not listed, were measured in some of the tests and were always strongly pressant.

Comment

As in many American Negroes, this patient's essential hypertension ran a rapid course over about eight years. It was complicated during the last three of these by the syndrome of malignant hypertension, which was atypical in several respects; cardiac and renal failure were only terminal events; encephalopathy was recurrent in two forms, both associated with severe increases of arterial pressure. A condition suggestive of hyperfunction of the adrenal cortex supervened and spontaneously disappeared; it was followed by a nephrotic syndrome of about one month's duration. Treatment wth antihypertensive drugs may have influenced the course, which, in perspective, exemplifies the problem of resistance to these agents.

Hexamethonium Resistance. — Resistance to ganglion blockers is a common and disconcerting problem in the treatment of severe hypertensive disease. These drugs seem to act by competitive inhibition of acetylcholine in autonomic ganglia. Synaptic blockade is more complete in some ganglia than in others. Since the action is competitive, it is always incomplete in some degree. Thus, doses of these drugs which will suppress

TABLE 2.—*Cardiovascular Reactivity (Millimeters of Mercury, Rise or Fall) At Various Stages of Diseases*

No. Fig.	Month	Avg. B.P. mm. Hg	Nitroprusside 1 γ/kg	Nitroprusside 1 γ/kg	Arterenol 4 γ	Arterenol	Serotonin 2 mg.	Serotonin	TEAC 2.5 mg/kg.
3	65	228/124					+34/56	+42/68	−12/2
5	66	200/138	−20/32		+58/42	+34/26	+16/6	+24/12	+20/8
7	72	240/146	−44/28	−46/32	+32/28		+24/30		+16/16
11	74	232/168	−28/16		+14/12	+18/16	−28/8-16/10		−16/12
18	86	286/200	−10/8	− 8/8	+14/8		− 4/4	−10/0	+ 4/4

Conditions under which test was done.
No. 3. All Drugs had been discontinued for 3 days.
No. 5. Almost refractory to hexamethonium continuous nitroprusside therapy until the day of the test. Patient in and out of encephalopathy several days before. Angiotonin response to 0.5 ml.-50/18.
No. 7. Nitroprusside infusion given up to 4 hours before the test; all other medication discontinued 2 days before. Angiotonin response to 0.5 mg.-40/22 mm. Hg.
No. 11. Ninth nerves had been sectioned 2 weeks before, hexamethonium discontinued 24 hours before test.
No. 18. Patient was comatose and died four hours later. She had a generalized convulsion during the test. Chlorpromazine (Thorazine) 25 mg. intramuscularly and nitroprusside were the medications used before the test.

orthostatic reflexes do not suppress a pressor response from increased intracranial pressure. This latter response is abolished by cord section or by high spinal anesthesia, in which the vasomotor block is apparently complete. It may be that the common failure of chronically administered blocking agents to decrease supine blood pressure reflects maintenance of vasomotor arterial tone by synapses which are inherently resistant to these agents, while the orthostatic hypotension common in these patients is attributable to persistent block of vasomotor nerve impulses.

If incomplete blockade were the mechanism underlying hexamethonium resistance, it would be expected that supine arterial pressure would be decreased by high spinal anesthesia. However, this procedure was not depressant in this patient or in four other patients who had become resistant to the supine depressant effect of hexamethonium. Further, the responses of the patient's blood pressure to tests doses of TEAC and serotonin were such as are observed in animals with low vasomotor tone and in dogs with acute or malignant experimental renal hypertension (Page and McCubbin [12]). That the limitation in depressor responsiveness is not due to structural changes is indicated by the fact that a directly acting vasodilator, sodium nitroprusside, is adequately depressant in patients made resistant to hexamethonium.

These observations favor the concept that hypertension in these patients is maintained in part by non-neural mechanisms. While these may be conceived of as intrinsic to the vascular tree, it would seem more likely that they represent activity of circulating pressor agents which, in patients with nephrosclerotic renal disease, might be of renal origin. This hypothesis envisions a shift in the balance of mechanisms which sustain hypertension from one in which vasomotor nerves contribute significantly toward one in which they contribute less, to a point where, as in the case of this patient, drugs such as hexamethonium and veratrum alkaloids lose their depressant effects. A like shift of mechanism was postulated previously from observations in a patient who was treated for hypertension with a sympatholytic agent, Dibenzylene phenoxybenzamine.[3] Should such a mechanism of non-neural hypertension be demonstrable, it would seem to us to be the crux of the etiologic, as it is also the nub of the therapeutic, problem of severe hypertensive disease.

It should be noted that resistance to drugs of the degree described above is not the rule. A minority of patients are fortunate enough to remain sensitive to both the supine and standing depressor effects of ganglion blockers; these, in general, have a more favorable course than the majority, who lose the supine but retain the standing depressor effect. This latter state is physiologically undesirable, since it reflects orthostatic decreases in venous return and cardiac output which are associated clinically with weakness and fatigability. However, even this abnormal hemodynamic state contributes to increased survival in patients with severe hypertensive disease.[11]

Resistance to Other Drugs.—The patient was resistant to other antihypertensive agents, including hydralazine and reserpine, which are commonly effective. She was also resistant to protoveratrine alone, or in combination with chlorpromazine, which was used ineffectively in her case and in others with the aim of controlling the emetic action of veratrum alkaloids. Also ineffective in her case were iproniazid and isoniazid, which were slightly depressant in other patients, and sodium azide, which has only a transient depressant effect. These three agents cannot be considered as potential antihypertensive drugs.

Ninth Nerve Section.—The possibility

that denervation of the carotid sinuses might enhance responsiveness to depressant drugs was considered in this case since it has this effect in dogs.[4] However, no distinct beneficial effect was demonstrated. The possibility that some effect was obtained was not excluded, since her severe and complicated illness prevented definitive observations.

Encephalopathy.—This assumed two forms. The one, which presented at first, was characterized by a progression from severe headache through restless drowsiness and vomiting to stupor. Whenever, in this situation, arterial pressure was sharply decreased toward normal by nitroprusside infusions, relief occurred within a hour or two and persisted as long as the pressure was controlled, with frequent lapses when pressure was allowed to rise sharply. The second form of encephalopathy was also associated with sharp rises of blood pressure; it was characterized by loss of vision and grand mal seizures which were associated with electroencephalographic abnormalities. The responses of this encephalopathy to decreased blood pressure was delayed and equivocal.

The sequence of events in the first form suggested that the encephalopathy, like that of Byrom's rats,[16] was associated with vasospasm, since decreased pressure promptly relieved it. In the second form, the slow response and the nature of the EEG suggested damage to cerebral tissues. Such damage seemed to be present on gross examination of the brain but was not verified microscopically. It seems likely that this second, convulsive, amaurotic form of encephalopathy is an intensification of the first, with some local damage, such as edema, again a situation demonstrated in rats with experimental hypertension. The absence of any association of these attacks with increased cerebrospinal fluid pressure accords with our previous experience.[16]

Complications of Drug Treatment.—These, in our patient, were not severe. One was the focal arteritis which developed during treatment with hydralazine. We have seen similar nodules in two other patients given hydralazine and have several times noted the occurrence of painful lesions in the region of the ankles; unfortunately, none of these lesions was examined microscopically, so their listing as complications of hydralazine therapy is incomplete. It should be noted that these manifestations are quite distinct from the arthritic and febrile syndrome associated with this drug.[1]

The pneumonic state which came on during the 75th month was associated with administration of large doses of hexamethonium and subsided when this drug was withdrawn. Pulmonary fibrosis was an important cause of death in patients with severe hypertension under treatment with hexamethonium.[17] It is assumed that it was this condition which had developed in our patient, but with the unusual characteristic that pulmonary signs remitted promptly when hexamethonium was discontinued and did not recur when the drug was given again. However, residual lesions of pulmonary fibrosis were demonstrated after her death, one year later.

Hypercorticoidism (?); Nephrotic Syndrome.—The development of potassium-resistant hypochloremic alkalosis, with facial rounding, facial and pectoral acne and hirsutism, and excretion of nearly neutral urine suggested hyperfunction of the adrenal cortex. This was not demonstrated and the condition did not persist, except as it may have been related to the adrenal hyperplasia noted at autopsy.

This obscure condition was followed by another complication, in the form of a nephrotic syndrome. For this also we are unable to account. A nephrotic state has been described as a complication of treatment with the methadione but not with the hydantoin anticonvulsant. In general, the nephrotic syndrome is associated

with primary glomerular rather than predominantly preglomerular renal vascular lesions. It may have been that the atypical course of nephrosclerosis in this case was such that there was disproportionate damage of glomerular vessels at this phase in her course. The renal histology suggested that the preglomerular vessels had sustained acute, necrotizing damage only shortly before her death.

Atherosclerosis.—At autopsy we were impressed by the relative absence of gross atherosclerosis in the coronary, aortic, and cerebral vessels. There were no distinctive characteristics of her serum lipoprotein and cholesterol concentrations which might be associated with protection from atheroma; β-globulin and β-liporprotein concentrations were not abnormally low. The only protective factor is apparently that common to premenopausal women.

Summary

Present relative success in the treatment of severe hypertensive disease with antihypertensive drugs does not resolve the problem of patients who do not respond to these agents. This problem is examined by a detailed report of the findings during two and one-half years of the life of a patient whose disease was resistant to treatment.

The drugs used were hydralazine, alone and in combination with hexamethonium and pentolinium; reserpine, thiocyanate, protoveratrine, alone and in combination with chlorpromazine, sodium azide, iproniazid, and isoniazid. Experience in this patient and in others shows that chlorpromazine does not protect against the emetic action of veratrum drugs and that azide, iproniazid, and isoniazid are not useful as antihypertensive drugs.

Denervation of the carotid sinuses was done with the hope of increasing sensitivity to the depressor effect of antihypertensive drugs. No beneficial effects were observed in this case. This experience does not constitute a crucial test of this procedure.

Hypertensive encephalopathy assumed two forms; at first, it was associated with severe headache, restlessness, and progessive blunting of consciousness, all of which were promptly relieved by decreasing the severely increased blood pressure toward normal with intravenous infusion of sodium nitroprusside. A second form appeared later in the course, in which unconsciousness followed on repeated grand mal seizures, which were often preceded by blindness; consciousness, in this form, was not promptly restored by nitroprusside infusion. This required maintenance treatment with an anticonvulsant drug.

The responses of blood pressure to drugs and to spinal anesthesia suggested that resistance to the depressor effect of ganglion blockers may be attributable to maintenance of the hypertension by some non-neural pressor mechanism. This last seems to be the nub of the problem of severe hypertensive disease.

Unexplained events in the course of her illness were a state suggestive of hyperfunction of the adrenal cortex, and, a little later, a transitory nephrotic syndrome. She also showed signs and symptoms of the diffuse pulmonary disease seen in patients given hexamethonium; this subsided when the drug was withdrawn, and the syndrome did not recur when the drug was given again, but residua of pulmonary fibrosis were found at autopsy one year later.

In spite of the severe malignant hypertension, present over a period of more than two years, only very mild evidences of atherosclerosis were demonstrable at autopsy in this young woman. The serum lipoprotein pattern had no distinctive characteristic which would explain this seeming protection against atheroma.

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Drug Therapy of Hypertension

IV. The Indications and Contraindications for Antihypertensive Drugs

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General Considerations

The majority of functional alterations resulting from prolonged or severe hypertension stem from damage to three important vascular beds, the brain, the heart, and the kidneys. When hypertension becomes sufficiently severe and/or is sustained for an adequate period of time, this in itself can produce the vascular deterioration that occurs in these areas.[1] It is rational to treat patients with severe disease, especially when complications exist which have resulted from the elevation in blood pressure. It also seems rational to treat patients with moderately severe disease. Here the objective is to prevent progression and the development of serious complications. Although the treatment of hypertension is still largely empirical, evidence is accumulating rapidly which indicates that the symptoms and complications resulting from severe and prolonged hypertension can be improved by effective reduction of blood pressure, using currently available antihypertensive agents. It follows naturally that the chief indications for antihypertensive agents is a significant elevation in diastolic blood pressure, particularly if there is evidence of vascular deterioration. There are few, if any absolute contraindications to this rule. Some relative contraindications will be discussed.

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Therapeutic Value of Antihypertensive Agents

Before accepting the statement that effective control of blood pressure is beneficial, one can ask, logically, what is the evidence? We will consider first a large group of patients with all grades of severity of hypertension and who have been followed in our clinics all over the past six years. Some of the commoner complications associated with the disease are recorded statistically in Table 1. This represents a group of patients from the private practice of the author and his associates * and from the cardiac clinics of the Jefferson Davis Hospital, the Veterans Administration Hospital, and the Hermann Hospital, Houston, Texas. It is obvious that these patients had relatively severe disease, since the incidence of complications is so high. The data (Table 1) indicate that both objective and subjective manifestations are improved greatly by antihypertensive therapy, regardless of the therapeutic program employed.

Patients with malignant hypertension provide a more rigid test, inasmuch as the prognosis of these patients when untreated is no better than the prognosis of the patient with cancer of the breast, stomach, or lung. Severe hypertension is a notorious cause of progressive vascular deterioration of the vascular systems in the brain, heart, and kidneys. Consequently the patient with malignant hypertension usually dies of cerebral hemorrhage, coronary occlusion, heart failure, or progressive renal failure. The last can be the most devastating, and least treatable, of all complications. However, if

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TABLE 1.—*Incidence of Some Symptoms and Signs in Patients with Hypertension and the Beneficial Effects of Antihypertensive Therapy*

Treatment Program	No. Pts. Treated	Bradycrotic* Response	Headache	Angina Pectoris	Congestive Heart Failure	Electrocardiographic Abnormality	Renal Damage	Funduscopic Changes	Cardiomegaly (X-Ray)
Rauwolfia alone	346								
No. with symptom			142	45	128	208	65	38	100
Per cent improved		65	70	38	16	7	0	5	20
Rauwolfia + hydralazine	15								
No. with symptom			4	1	8	12	9	5	11
Per cent improved		73	50	0	13	8	11	20	0
Rauwolfia + pentolinium	75								
No. with symptom			23	7	23	52	8	12	58
Per cent improved		67	78	71	65	40	37	58	38
Rauwolfia + mecamylamine	80								
No. with symptom			52	10	27	67	61	17	48
Per cent improved		49	71	80	81	25	25	59	31

* A decrease in the pulse rate of 10 beats per minute or more.

treated early and effectively, such complications can be prevented frequently, even after the onset of the malignant phase of the disease.[1]

Table 2 shows a comparison of our results with those of Schroeder, Morrow, and Perry.† In untreated patients with malignant hypertension who were not in uremia, the one-year survival rate was 27% during 1949 to 1952 at the Jefferson Davis Hospital. This compares with the observations of Schroeder and co-workers, who observed a survival rate of 11% in untreated patients. Schottstaedt and Sokolow [3] reported a survival rate of 12% for 18 months.

after severe renal damage has occurred, the prognosis decreases considerably. The results of Schroeder and co-workers, covering a larger series of patients, are similar (Table 2). It is logical to conclude that adequate antihypertensive therapy in patients with severe disease makes it possible to improve greatly the prognosis even though renal damage already exists (indicated by an elevated blood urea nitrogen). However, the severer the renal damage, the poorer the prognosis. Consequently, the higher the blood urea nitrogen prior to treatment, the less effective the therapy.

TABLE 2.—*Survival Rate in Patients with Malignant Hypertension*

	No. Patients Treated	Survival for 1 Yr. or More		No. Patients Treated	Survival for 2 Yr. or More	
		No.	Per Cent		No.	Per Cent
Hypertensive clinic (Jefferson-Davis)						
Untreated (nonuremic)	22	6	27	22	2	9
Treated						
Azotemia* (nonuremic)	15	9	60	5	3	60
Normal B.U.N.	11	10	91	11	8	73
Uremia	28	0	0	--	--	--
Schroeder, Morrow, and Perry†						
No treatment	28	3	11	28	3	11
Treated						
Uremia	10	0	0	--	--	--
Azotemia‡ (nonuremic)	25	19	76	46§	27	59
Normal N.P.N.	23	18	78	23	17	74

* B.U.N. (blood urea nitrogen) more than 20 mg. per 100 cc.
† References 1 and 2.
‡ N.P.N. 30-60 mg. per 100 cc. before treatment.
§ 21 additional patients included in this group (2) who were not included in original publication (1).

In those patients with malignant hypertension who were started on treatment at the Jefferson Davis Hospital between 1952 and 1953, the survival rate was 91% in those patients who exhibited less severe renal damage (indicated by a normal blood urea nitrogen prior to therapy). However, in 15 patients in whom the blood urea nitrogen was elevated, the survival rate was only 60%. In the patients who were in uremia, therapy did not improve the prognosis. The mortality was 100%. This indicates that

† References 1 and 2. Schroeder, H. A.: Personal communication to the authors.

Pharmacodynamics of Antihypertensive Agents

During the past decade, many pharmaceutical agents have become available which act upon the autonomic nervous system to block impulses traveling from the brain to the small blood vessels throughout the body. These compounds make it possible to reduce the blood pressure in nearly all patients, regardless of the degree of elevation or the underlying cause. This is accomplished by depressing the number of vasoconstrictor impulses which reach the blood vessels via the sympathetic nervous system.

Drugs available for this purpose can be divided into centrally acting agents, such as the Rauwolfia compounds and hydralazine; ganglionic blocking agents, such as hexamethonium, pentolinium, and mecamylamine, and peripherally acting agents, such as phenoxybenzamine (Dibenzyline) (Fig. 1).

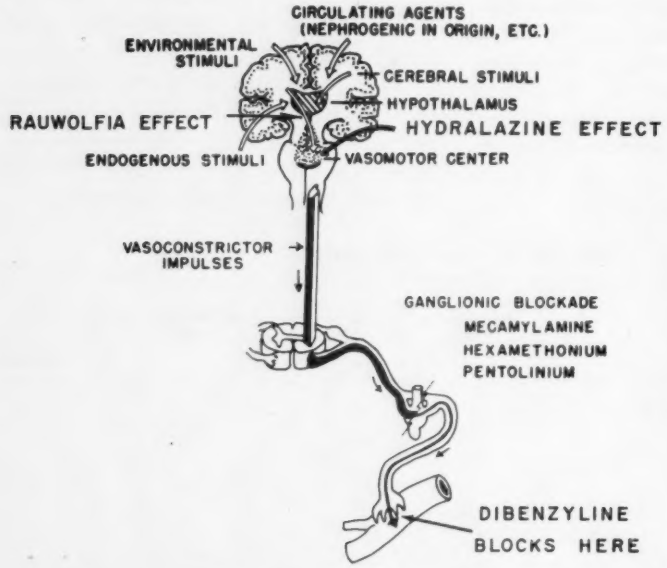


Fig. 1.—Diagrammatic representation of the pharmacodynamics of antihypertensive drugs, showing the point of blockade of vasoconstrictor impulses within the sympathetic nervous system. (Adapted from Figure 2, Moyer, J. H., and others: A. M. A. Arch. Int. Med. 96:530, 1955.)

The general therapeutic program that we use is outlined in Table 3. It is apparent that the severity of the elevation in diastolic blood pressure is the most important single finding to guide the therapeutic program, since this can be treated effectively in virtually all patients who have not already developed renal decompensation. The more numerous and the severer the complications associated with the hypertensive vascular disease, the more urgent is the necessity to start effective therapy.

Patients with milder disease are started

TABLE 3.—*Suggested Therapeutic Approach to the Treatment (Outpatient) of Hypertension*

Severity of Hypertension	Therapy
Mild (diastolic pressure=100 to 130 mm. Hg)	
Labile	Rauwolfia*
Fixed diastolic	Rauwolfia* alone or with hydralazine† or ganglionic blocking agents‡
Severe (diastolic> 130 mm. Hg)	Rauwolfia plus ganglionic blocking agents‡ or phenoxybenzamine (Dibenzyline)§
Hypertensive emergency	Parenteral reserpine; add parenteral hydralazine or veratrum if response to reserpine is inadequate

* Daily dose of 4 mg. alseroxylon, 300 mg. of whole root, or 1 mg. of reserpine.

† Start with 25 mg. after each meal and at bedtime and gradually increase to a maximum of 600 mg. or until blood pressure controlled.

‡ Start on small doses of ganglionic blocking agent, such as 125 mg. hexamethonium after each meal and at bedtime, 40 mg. of pentolinium (Ansolysen) after each meal and at bedtime, or 2.5 mg. of mecamylamine (Inversine) after breakfast and supper. Increase progressively until blood pressure is adequately reduced in the upright position.

§ Start with 5 mg. after breakfast and supper and progressively titrate the dose in 5 mg. increments.

on Rauwolfia alone. If they are unresponsive to this agent, hydralazine or a ganglionic blocking agent may be added, depending on the urgency for reduction of blood pressure. Rauwolfia has a stabilizing effect on the blood pressure. This is notable when the results with Rauwolfia plus ganglionic blocking agents are compared with the results from ganglionic blocking agents alone (Fig. 2). This is due, in part, to the so-called "tranquilizing" effect on psychodynamics. In the patient with severe disease, Rauwolfia is started initially and followed within several days by a ganglionic

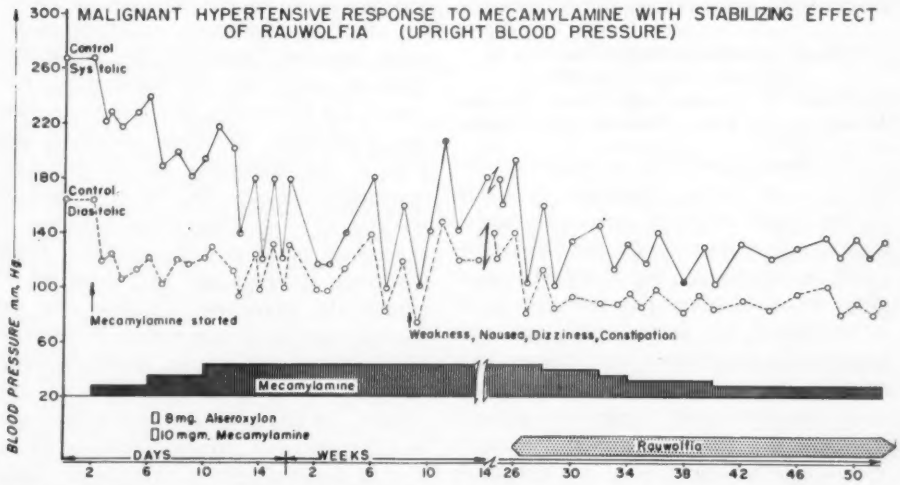


Fig. 2.—The blood pressure in this patient fluctuated excessively during treatment with the ganglionic blocking agent (mecamylamine) alone. After the addition of Rauwolfia to the therapeutic program, the blood pressure was much better stabilized and the dose of the ganglionic blocking agent could be reduced significantly.

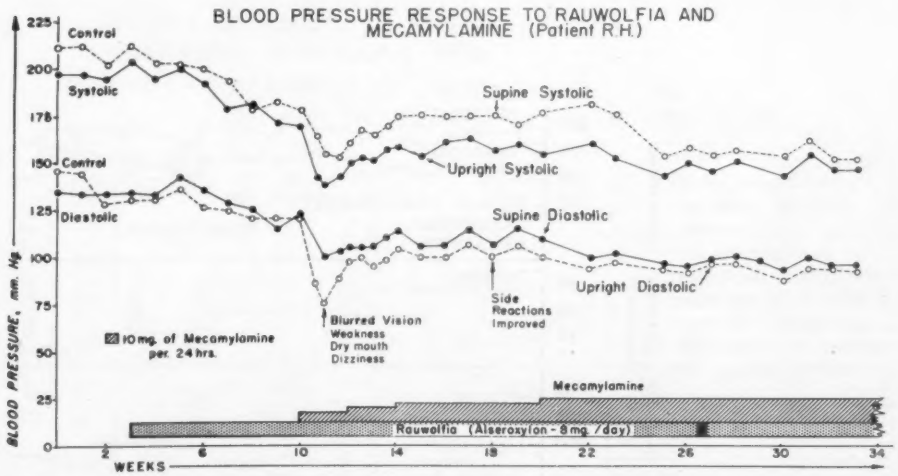


Fig. 3.—Method of administering the therapeutic agents in a patient with severe hypertension: The Rauwolfia compound is started initially. After the complete therapeutic effect of this drug alone has been obtained, a ganglionic blocking agent is given, starting with small doses and progressively increasing the dose until the desired reduction in blood pressure has been obtained.

blocking agent (Fig. 3). Our experience indicates that neither veratrum nor hydralazine is beneficial in patients with severe hypertension. The ganglionic blocking agents are added in a titration procedure, and the dose is gradually increased until the blood pressure is controlled within the desirable range. The details of this procedure will be discussed elsewhere in this symposium.

Indications and Contraindications of Antihypertensive Agents

Treatment of Patients with Renal Damage Associated with Severe Essential Hypertension

The effect of severe hypertension on the kidney is particularly important, since this is one organ in which symptoms cannot be reversed; neither can the functioning capacity be improved, after a certain critical phase for each patient has been passed. It is established that severe and progressive hypertension can produce renal damage, particularly after it has reached the malignant phase ‡ of the disease. Progressive deterioration of the kidney will occur frequently within a period of three to six months in the patient who develops malignant hypertension (Fig. 4). It is reasonable to assume that a more insidious type, and degree, of vascular damage will occur in the patient with less serious hypertensive vascular disease, despite the fact that the hypertensive state may exist for years without producing observable renal damage.

The patient presented in Figure 4 was a Negro in whom we were able to follow the effect of malignant hypertension on renal function, measured by glomerular filtration rate and renal blood flow. Repeated renal function studies were done over a period of 10 months on this patient prior to the availability of effective antihypertensive agents for the treatment of this type of case. Progressive reduction in glomerular filtration rate and renal blood flow were apparent, and by the end of 10 months the glomerular filtration rate decreased from 90 cc. per minute to approximately 40 cc. per minute, while the renal blood flow decreased from 900 cc. per minute. At this point the patient developed manifestations of uremia, accompanied by central nervous system symptoms. Renal function studies were repeated two months later. At this time glomerular filtration rate had decreased to 30 cc. per minute and renal

‡ Criteria: severe diastolic hypertension, retinal hemorrhage, and papilledema.

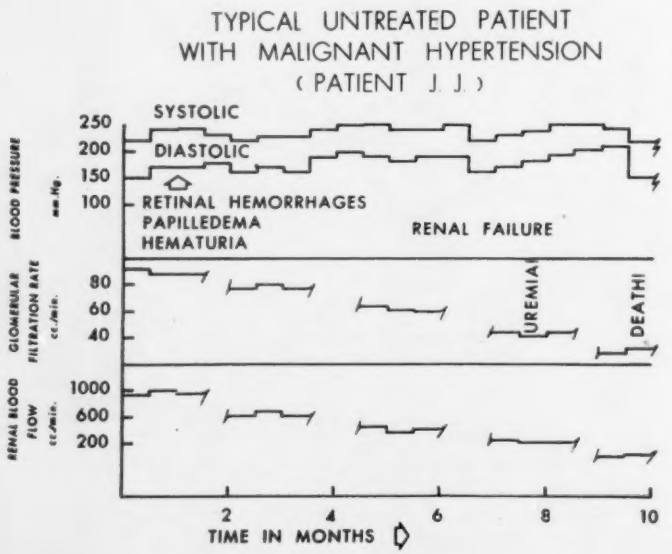


Fig. 4.—Typical effect of malignant hypertension on renal function. There is progressive deterioration of the kidney as indicated by reduction in glomerular filtration rate and renal blood flow followed by uremia and death.

blood flow to approximately 150 cc. per minute. Shortly after the latter study the patient died of uremia. It is possible today to treat this type of patient effectively and probably to arrest the renal vascular deterioration prior to the development of uremia (Figs. 5 and 6).

Figures 5 and 6 present observations on renal function in two patients with malignant hypertension, before and after effective antihypertensive therapy. Differential renal function studies were performed over a period of six months; during this time these patients were not treated with effective antihypertensive agents. A progressive reduction in glomerular filtration rate, as well as in renal blood flow, was noted in both of these patients. This indicates that progressive renal damage occurred before therapy was instituted. The patients were then treated with Rauwolfia, plus a ganglionic blocking agent, which reduced their blood pressure effectively. After 12 months of treatment, the renal vascular deterioration was arrested completely, and the glomerular filtration rate was essentially the same as it had been prior to institution of therapy. This indicates that vascular deterioration can be arrested, but it does not improve significantly and certainly does not return to normal. This is a strong plea for effective therapy in patients with severe hypertension, i. e., before they have developed renal damage beyond the point of no return.§

Most patients who have moderately severe to severe hypertension for a prolonged period of time will usually exhibit variable degrees of renal damage. This must be considered before instituting antihypertensive therapy. Effective reduction of blood pressure will usually prevent progressive anatomical damage to the kidney, but the physiology of renal function is such that some reduction in glomerular filtration rate will usually accompany the initial reduction of blood pressure. This is only temporary and minimal, returning to control values after renal hemodynamic readjustment takes place if the blood pressure is not reduced excessively. As a general rule, the less the renal damage prior to induction of therapy, the better the patient will tolerate blood pressure reduction. For example, if the glomerular filtration rate is adequate and the blood urea nitrogen is normal the blood pressure can be reduced to normotensive levels (130-150/80-100) without danger of renal decompensation. However, if glomerular filtration rate is severely depressed, indicating marked renal damage, prior to

§ References 1-3.

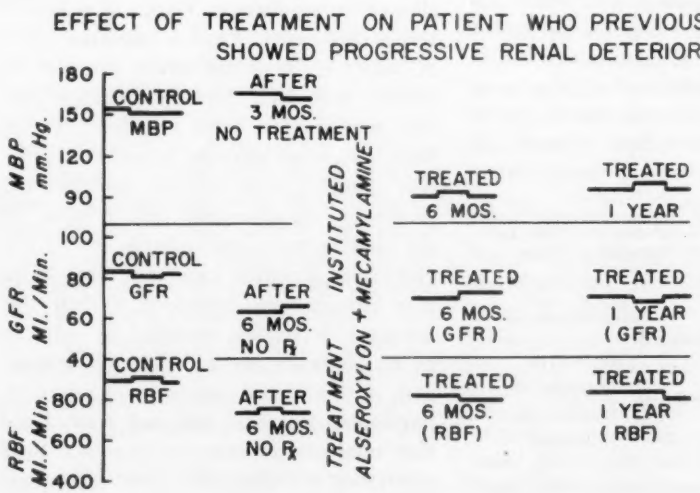


Fig. 5.—When the patient with malignant hypertension who shows progressive renal deterioration is given adequate antihypertensive therapy, the process is arrested. Although glomerular filtration rate and renal blood flow are not further depressed at the same time, there is no return of these functions to normal.

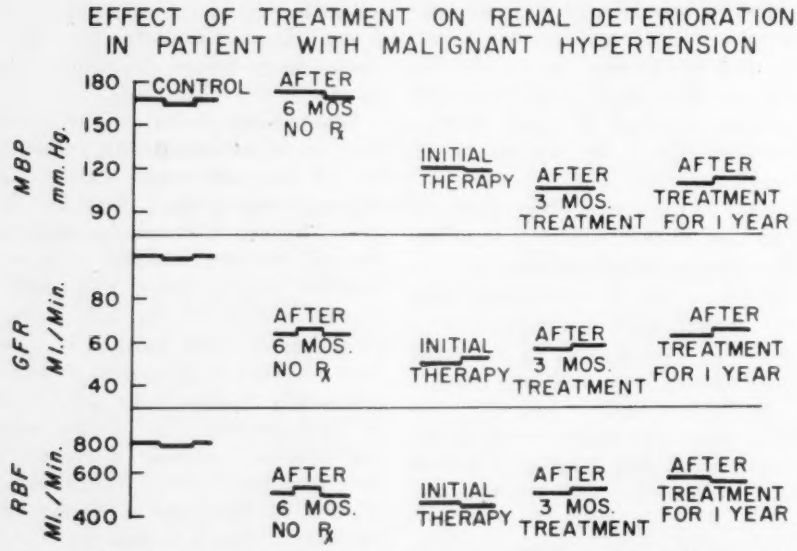


Fig. 6.—Effective treatment of a patient who showed progressive renal deterioration prior to adequate antihypertensive therapy. Following therapy for one year there was no evidence of further damage to the kidney.

the induction of therapy, even a slight reduction in glomerular filtration rate may be deleterious. In such patients, it is essential that the blood pressure be reduced very slowly and also to keep a close observation on the blood urea nitrogen. This is by far the most valuable laboratory aid (Table 4) for guiding the therapist concerning the degree of blood pressure reduction which will be tolerated by the patient with preexistent renal damage. Table 4 presents the general range to which the blood pressure can be reduced in most cases without depressing renal function. It is obvious that the greater the elevation of blood urea nitrogen, the less effectively the blood pressure can be reduced. When the blood urea nitrogen is above 40, repeated determinations must be made while the blood pressure is being reduced.

TABLE 4.—*Approximate Degree of Blood Pressure Reduction (Upright) That Can be Tolerated—Based on Amount of Preexisting Azotemia*

Blood Urea Nitrogen, Mg./100 Cc.	Upright Blood Pressure Reduction
Normal	130-150/80-100
30 to 60	150-170/100-110*
60 to 100	180-190/110-120*
100	No reduction

* Do not reduce blood pressure further if B.U.N. rises.

The blood pressure should always be regulated in the upright position. When there is evidence that the blood urea nitrogen is rising, the blood pressure can not be reduced any further; in fact, it should usually be allowed to rise slightly. Thus, a paradoxical renal effect exists. From a functional point of view, reducing the blood pressure in patients who have severely damaged kidneys may depress renal function. At the same time, if an adequate reduction in pressure can be achieved, this will prevent progressive renal vascular deterioration. If the blood pressure is reduced excessively, glomerular filtration rate and renal blood flow may remain depressed. When this occurs, it is readily combated by infusion of a vasopressor agent. When this is done, and as the blood pressure is elevated, glomerular filtration rate and renal blood flow return toward the control values. Such a response is depicted in Figure 7.

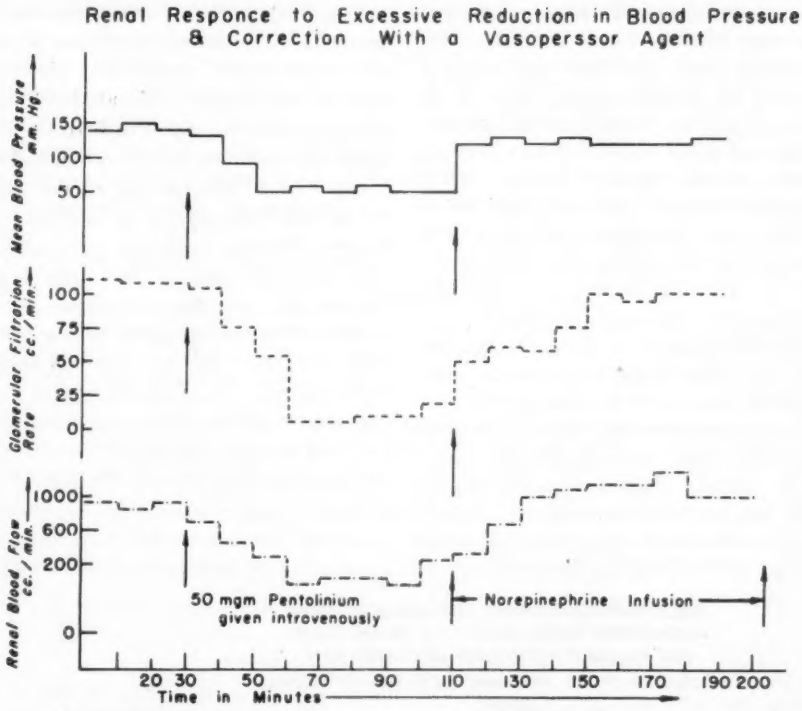


Fig. 7.—When glomerular filtration rate and renal blood flow are severely depressed due to excessive reduction in blood pressure, this can be corrected easily by increasing the blood pressure with vasopressor agents such as phenylephrine (Neo-Synephrine), arterenol (norepinephrine), or metaraminol (Aramine).

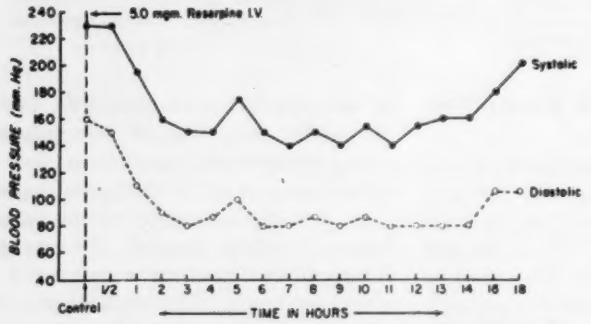
Hypertension Associated with Primary Renal Disease

The patient with primary renal disease may benefit from blood pressure control if severe hypertension becomes an important component of his disease. Let us consider some observations made on the treatment of renal arterial (arteriosclerotic) occlusive disease, associated with severe to malignant hypertension. These patients respond as well as patients with severe essential hypertensive vascular disease, provided the blood pressure is not reduced excessively. Such a case is summarized in Figure 8. This patient developed marked atherosclerosis of the aorta, which involved also the right renal artery and was followed by thrombus formation which completely occluded the right renal artery. The left renal artery was not involved. When admitted to the hospital, the patient had marked encephalopathy, retinal hemorrhages, papilledema, and convulsions as a result of malignant hypertension, probably secondary to the ischemic kidney (Goldblatt kidney). He was given parenteral reserpine, in a dose of 5 mg. every six hours. This reduced the blood pressure effectively; following this most of the cerebral manifestations subsided. He was changed gradually to a combination of oral Rauwolfia and a ganglionic blocking agent, mecamylamine (Inversine). After blood pressure control was achieved, a homograph replacement of the aorta was done.‖ He has since been well regulated

‖ Homograph replacement surgery was performed by Dr. Michael F. DeBakey and Dr. Oscar Creech.

for a period of one year and is in full-time employment with the Texas Company. His blood pressure and renal functional response to therapy are summarized in Figure 8. It is obvious that no return of renal function was achieved in the occluded kidney (right). However, in the opposite kidney (left), glomerular filtration rate and renal blood flow, which were depressed to less than 50% of normal for one kidney prior to therapy, increased gradually so that now they are approximately normal. His blood urea nitrogen decreased from 70 to 30 mg. per 100 cc. Undoubtedly the depression in function in the unoccluded left kidney was due to severe vasoconstriction, intrarenal hemorrhages, and acute vascular damage rather than to chronic deterioration which decreased the functional capacity of this kidney. Since the process was relatively acute, it was reversible. Had the hypertension and increased sympathetic vasoconstrictor response been permitted to persist, progressive renal failure would have developed, provided the patient did not first die of cerebral manifestations. Furthermore, if the initial depression in renal function had been due to chronic deterioration of the kidney, the marked improvement in function which followed therapy would not have occurred. This was the case in the right kidney. Despite the fact that circulation was reestablished following aortic homograph replacement, there was no return in function in this kidney. This case is a typical clinical counterpart of the "ischemic kidney" that has been produced in dogs.[4] Therefore, we can conclude that even in the patient with primary renal disease and hypertension secondary thereto, benefit can be derived from effective antihypertensive therapy.

BLOOD PRESSURE RESPONSE TO 5 MGM. OF RESERPINE ADMINISTERED INTRAVENOUSLY TO A PATIENT (G.L.M.) WITH MALIGNANT HYPERTENSION ASSOCIATED WITH OCCLUSION OF THE ABDOMINAL AORTA AND LEFT RENAL ARTERY



RENAL FUNCTION RESPONSE FOLLOWING HOMOGRAPH IN PATIENT WITH GOLDBLATT KIDNEY

	Glomerular Filtration Rate ml/min.		Renal Blood Flow ml/min.	
	Right (occluded)	Left	Right (occluded)	Left
Control	0	25	0	130
Blood Pressure Rx.	0	35	0	200
Homograph				
1 month	0	45	0	425
8 month	0	60	0	725

Fig. 8.—Patient with atherosclerosis of the aorta which resulted in complete occlusion of the right renal artery. This was followed by the malignant hypertensive syndrome. The artery to the contralateral (left) kidney was not involved, but because of the malignant hypertension the kidney showed a marked reduction in glomerular filtration rate and renal blood flow. Following adequate antihypertensive therapy, renal function improved in the unoccluded kidney, and the general vascular deterioration was also arrested. The response to therapy was also reflected in reversal of papilledema and complete clearing of retinal hemorrhages.

Occasionally patients with nephritis may develop severe hypertension which aggravates the renal damage. These patients will benefit from antihypertensive therapy. The degree of blood pressure reduction that these patients will tolerate is dependent upon the degree of renal decompensation, and the same principles apply as outlined in Table 4.

PATIENT 4.¶—This patient is a 5-year-old white boy who developed a typical nephrotic syndrome at the age of 18 months, associated with massive edema and proteinuria, hypoproteinemia, and hypercholesteremia. Thereafter, the patient had intermittent edema for two and one-half years without hypertension. However, at the age of 4 years the patient had a spontaneous remission with diuresis and has remained free of edema to date. However, he has had polyuria and also polydypsia, with a fixed specific gravity of the urine. One year ago he was found to have a blood pressure of 270/180 mm. of Hg and was referred for study.

Physical examination revealed a white, pale, thin child who appeared chronically ill. His weight was 16 kg. The blood pressure was consistently elevated, ranging between 240 and 280 mm. of Hg systolic and 160 to 190 mm. of Hg diastolic. A phentolamine (Regitine) test was negative. Serum electrolytes were within normal limits. The blood urea nitrogen was 40 mg. per 100 cc. The urinary sodium: potassium ratio was normal. An intravenous pyelogram revealed normal filling of the calyces and no evidence of obstruction. Differential renal function tests were done at this time, and when corrected to 1.73 sq. m. body surface the glomerular filtration rate was 51 cc. per minute; the renal plasma flow was 155 cc. per minute, and effective renal blood flow was 231 cc. per minute. This represents marked renal damage.

Following parenteral reserpine, a 60 mm. of Hg fall in mean arterial blood pressure, from 210 to 150, was seen. At this time the glomerular filtration rate and renal blood flow were reduced to 20%. The patient was then given oral reserpine, 0.5 mg. three times a day. The blood pressure reduction was not considered adequate, and chlorisondamine (Ecolid) was started. The patient received 6.2 mg. three times a day initially, and this was increased in a stepwise fashion until he was receiving 50 mg. three times a day. This dosage has been continued for the past 12 months, and the blood pressure has remained in the range of 130 to 160 mm. of Hg systolic and 80 to 118 diastolic. The blood urea nitrogen has varied between 20 to 50 mg. per 100 cc., with no tendency to progressive rise. The renal functions were studied after four months of combined therapy and revealed a glomerular filtration rate of 41 cc. per minute, a renal plasma flow of 196 cc. per minute, and an effective renal blood flow of 350 cc. per minute. The patient feels fine, and the constipation is readily controlled with cathartics when necessary. The polyuria and fixed specific gravity of the urine are unchanged, and there has been very little change in weight.

BLOOD PRESSURE RESPONSE TO ORAL RESERPINE AND SU 3088 THERAPY

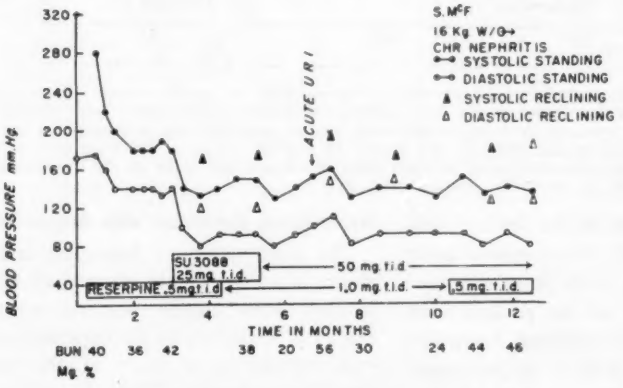


Fig. 9. — Blood pressure response to reserpine and a ganglionic blocking agent, chlorisondamine (Ecolid), in a patient with severe malignant hypertension due to primary renal disease. See text for description.

¶ Presented through the courtesy of Dr. William Daeschner, Dept. of Pediatrics.

Hypertension Associated with Heart Failure

Patients with heart failure usually improve rather markedly with effective reduction in blood pressure, particularly with the use of ganglionic blocking agents. For ex-

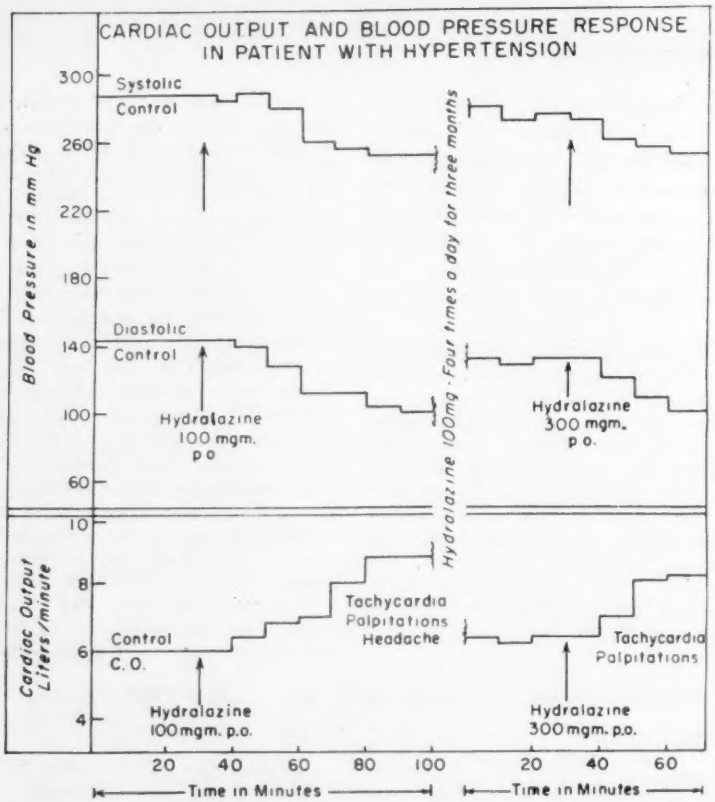


Fig. 10.—Effect of hydralazine (Apresoline) administration on cardiac output. There is a sharp increase in cardiac output as the flood pressure decreases. In a patient with coronary artery disease, this can cause coronary insufficiency, angina pectoris, and occasionally a myocardial infarction. The cardiac response can usually be blocked if one of the Rauwolfia compounds is given for an adequate period of time prior to the administration of the hydralazine. (Moyer, J. H.: A. M. A. Arch. Int. Med. 91:419, 1953.)

ample, in Table 1, 65% of the patients with heart failure showed improvement after institution of therapy with Rauwolfia and pentolinium and 81% of the patients with heart failure and who received Rauwolfia and mecamylamine showed improvement. Very frequently patients who have become resistant to diuretics and digitalis therapy respond adequately after effective blood pressure control is achieved with ganglionic blocking agents plus Rauwolfia.

Rauwolfia, alone and in combination with hydralazine, exerts relatively little beneficial effect in this respect; probably the patients who respond to this therapy are not as severely affected, and hypertension per se is not of great importance in the pathogenesis of their heart failure.

Hypertension Associated with Angina Pectoris

The combination of Rauwolfia and ganglionic blocking agents is very effective in patients with angina pectoris when the angina is secondary to the hypertension. At least two-thirds or more of the patients show improvement (Table 1) up to complete relief of this symptom.

Patients with angina pectoris or coronary artery disease should not receive hydralazine without the concurrent use of Rauwolfia, since this drug stimulates the sympathetics to the heart and causes a sharp increase in cardiac output, thus producing coronary insufficiency (Fig. 10). The cardiac effect of hydralazine is blocked in many patients if they are given Rauwolfia for one to two weeks before the hydralazine is administered.

Hypertension Associated with Cerebrovascular Sclerosis

Cerebrovascular disease is not a contraindication to antihypertensive drugs. If care is exercised in dosage in patients with cerebrovascular disease and excessive reductions of blood pressure are avoided, cerebral ischemia and insufficiency do not become a problem. In our experience, when a cerebrovascular accident has occurred during antihypertensive therapy it has almost invariably followed a sudden rise in blood pressure due to breakthrough of the blood pressure regulation. We have observed cerebral complications only following an excessive reduction in blood pressure in two patients. In one of these a hemiplegia developed which was transient and cleared up within several minutes.

Hypertension in the Elderly Patient

The elderly hypertensive patient should be managed just as the younger patient. When the diastolic blood pressure is elevated, this should be treated. The clinician can expect about the same response in these patients (Table 5) as in younger patients with hypertensive vascular disease.

The problem of treatment of patients with systolic hypertension without concurrent diastolic rise is still debatable, and one which the author does not feel qualified to discuss. Needless to say, it is not possible to reduce the blood pressure effectively in these patients with the use of milder antihypertensive agents, although symptomatic improvement can often be obtained. Reduction in the systolic pressure per se would largely be contingent on reducing cardiac output (stroke volume), which does not seem to be rational, although this effect would decrease the intra-arterial pressure thrust during systole and thus reduce some of the symptomatology and possibly the incidence of ruptured peripheral vessels. However, if the patient has both systolic and diastolic hypertension, he should be treated as outlined above.

The Hypertensive Emergency

Reserpine, in adequate parenteral dosage, is probably the most useful antihypertensive agent available for the treatment of hypertensive emergencies. When administered parenterally, it is potent, in contrast to the response after oral administration. However, there is a latent period of about one to two hours before the blood pressure decreases following either intravenous or intramuscular administration. If immediate reduction in blood pressure is required, a more rapidly acting drug is indicated.

TABLE 5.—*Comparison of Symptomatic Improvement in the Aged Patient (Above Age Sixty) with Hypertension and the Over-All Group (All Ages) of Patients with Hypertension*

	Per Cent Showing Improvement					
	"Average Hypertensive Patient"*			"Elderly Hypertensive Patient"†		
	Rauwolfia Alone	Rauwolfia + Hydralazine	Rauwolfia + Mecamylamine	Rauwolfia Alone	Rauwolfia + Hydralazine	Rauwolfia + Mecamylamine
Symptom or sign						
Headache	70	50	49	50	67	35
Angina pectoris	38	0	80	29	0	100
Abnormal ECG	7	8	25	15	8	41
Renal damage	0	9	25	0	17	45
Funduscopic changes	5	20	59	0	9	11
X-ray changes	20	0	31	22	0	45

* Values for patients with hypertension of all ages.
† Patients above the age of 60.

Under these circumstances, a ganglionic blocking agent or a veratrum extract may be used initially, the reserpine being administered at the same time for its long-term effect. Following the initial reduction in blood pressure with the ganglionic blocking agent, the patient can usually be maintained with parenteral reserpine alone.

We have studied the response to parenteral reserpine in three different groups of patients. They include hypertensive emergencies associated with (1) severe essential hypertension (Fig. 11), (2) toxemia of pregnancy (Fig. 12), and (3) severe hypertension of renal origin, such as acute nephritis (Fig. 13), and patients with renal

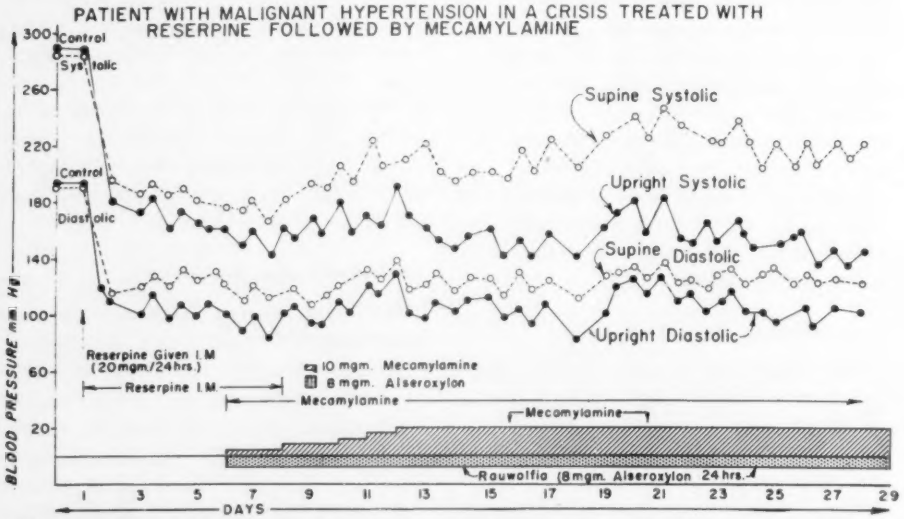


Fig. 11.—Patient with malignant hypertensive encephalopathy who required parenteral reserpine for initial reduction in blood pressure. After the blood pressure was regulated and the encephalopathic manifestations cleared, the patient was transferred slowly to a combination of Rauwolfia and a ganglionic blocking agent (mecamylamine) administered orally.

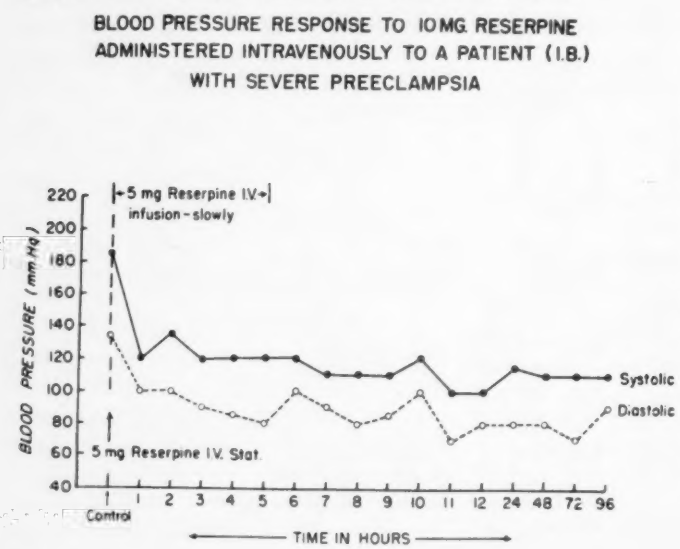


Fig. 12.—Blood pressure response in a patient with eclampsia. Over 90% of patients with hypertension due to toxemia of pregnancy will obtain a similar reduction in blood pressure following parenteral administration of reserpine. When hydralazine is given in combination with reserpine, the response rate approaches 100%. (Hughes, W. M.; Moyer, J. H., and Daeschner, W. C., Jr.: A. M. A. Arch. Int. Med. 95:563, 1955.)

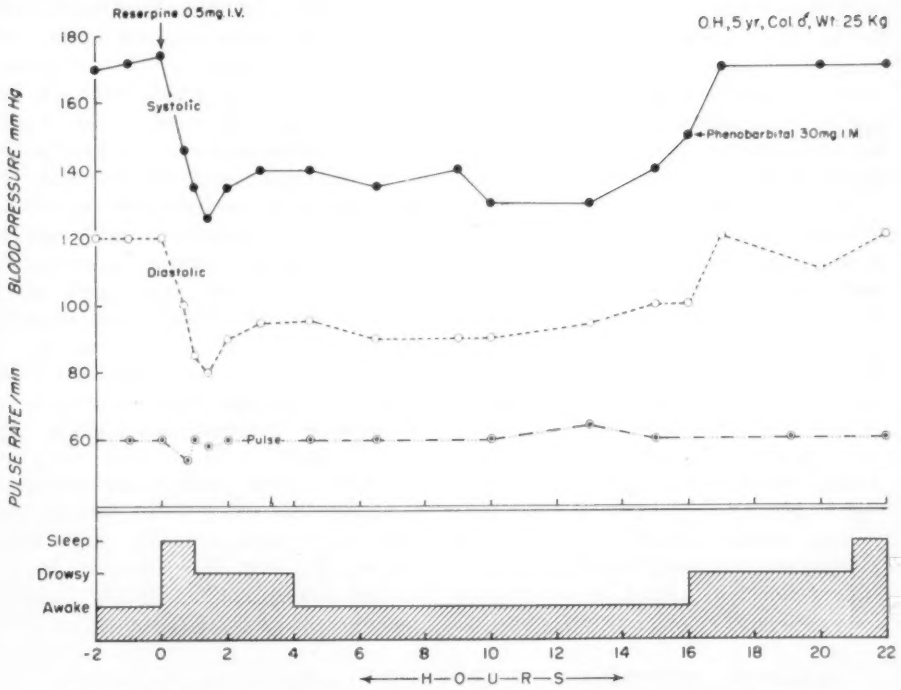


Fig. 13.—Blood pressure response to the administration of reserpine in a patient with acute glomerular nephritis and hypertension. The blood pressure could be well regulated with this therapeutic approach, and recovery was uneventful.

vascular occlusion (Fig. 8). The results achieved in these patients indicate that reserpine, when administered parenterally, is a relatively potent antihypertensive agent (Fig. 11), and there are few hypertensive patients who do not obtain a significant reduction in blood pressure. The antihypertensive effect is manifested in the recumbent as well as in the upright position, an attribute of considerable importance in the acutely ill and bedfast patient. The slow decrease in blood pressure plus the relatively rare instances of excessive reduction permits effective and safe therapy without particularly close supervision by medical and nursing personnel. Treatment of hypertensive emergencies with reserpine given parenterally seems to be most useful on a short-term basis, after which the therapy can be changed to effective medication given orally. This change is relatively easy, since the blood pressure control which has been established with the parenteral reserpine is lost slowly after the reserpine is discontinued. This gives us time for titration of the dose of the oral drug without a loss of blood pressure control.

Hydralazine is of limited value for the treatment of hypertensive emergencies and is confined primarily to use in acute glomerular nephritis and toxemia of pregnancy. In these disease entities it presents some specificity of action. Best results are obtained when this drug is used in conjunction with reserpine and given parenterally. The onset of action (15 to 20 minutes) is much more rapid than after the administration of reserpine alone. Therefore, it is given in situations where rapid onset of action is necessary or in patients who do not respond adequately to reserpine alone. While patients will respond to reserpine alone, hydralazine should be added to the regimen when a more rapid

effect is desired and/or when a more marked fall in blood pressure is needed. Even though hydralazine alone is effective in those patients, reserpine counteracts the tachycardia of hydralazine and aids in maintaining the normotensive state as well as in providing sedation.

When reserpine is ineffective in patients other than those with primary renal disease, a ganglionic blocking agent, such as hexamethonium, pentolinium, or mecamylamine, should be used either alone or in combination with reserpine (Fig. 14). When given intramuscularly, they are safe and usually effective therapeutic agents, and the danger of excessive reduction in blood pressure is not a problem. The frequency of administering intramuscular ganglionic blocking agents depends on the time that the blood pressure remains reduced. As soon as the hypertensive emergency is under control, the patient should be started on oral therapy. Care must be exercised in reducing the blood pressure in patients with renal failure, lest the renal function be impaired further. A systolic blood pressure of 170 to 180 mm. of Hg seems to be a safe level. If the blood pressure is reduced excessively, glomerular filtration rate in the kidneys becomes depressed markedly. Should this occur, it can be corrected by the administration of a vasopressor agent such as arterenol (norepinephrine) or any other readily available vasopressor agent which can be given intravenously or intramuscularly.

If ganglionic blocking agents are also ineffective, one can then use intravenous alkavervir or protoveratrine. Veratrum extracts (alkavervir or protoveratrine) are the most potent antihypertensive agents available today, and it is rare that a patient will not respond to these drugs given parenterally (Fig. 14). However, because of their potency and the difficulty of regulation of the blood pressure with these agents,

MALIGNANT HYPERTENSIVE ENCEPHALOPATHY - UNRESPONSIVE TO RESERPINE AND MECAMYLAMINE - TREATED WITH VERATRUM, GIVEN PARENTERALLY.

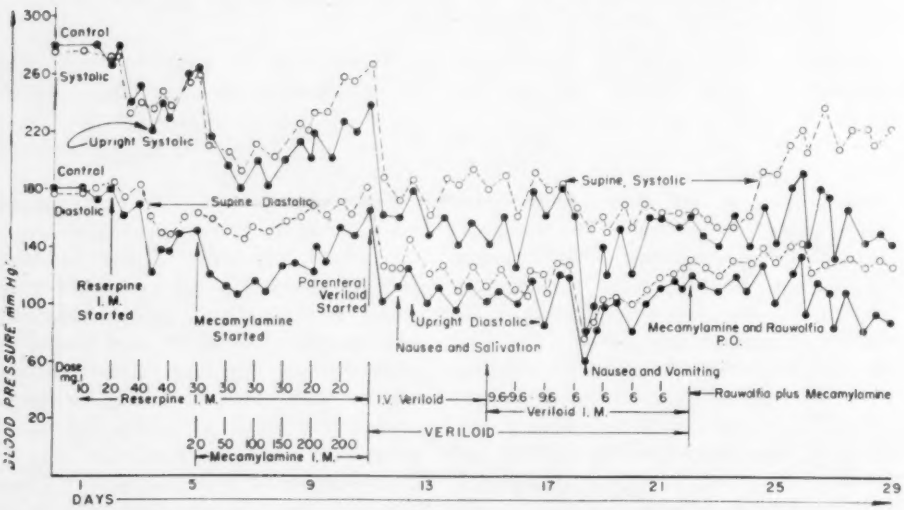


Fig. 14.—Treatment of a hypertensive crisis in a patient who did not obtain an adequate response to reserpine or to ganglionic blocking agents administered parenterally. A sharp and consistent reduction occurred when veratrum was administered intravenously, but nausea was seen. The blood pressure was controlled with parenteral veratrum; following this the cerebral manifestations cleared up. The patient was then transferred to a combination of Rauwolfia and mecamylamine given orally. On this combination, the blood pressure reduction was primarily in the orthostatic position, in contrast to the response when reserpine was given, as well as when the alkavervir (Veriloid) was given by continuous infusion.

they should be used only in those patients who do not respond to simpler methods of treatment.

Phenoxybenzamine is an effective adrenergic blocking agent which can be given intravenously. However, because of the complete blockade produced by this drug so that vasopressor agents are ineffective, it is generally inadvisable to use this blocking agent when given by the parenteral route. Should excessive reduction in blood pressure occur with the use of phenoxybenzamine, an effective antidote is not available. The very potency of this drug and its ability to block off the sympathetic nervous system completely limit its usefulness for the treatment of hypertension when parenteral administration becomes necessary.

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A Method for Administering the Antihypertensive Agents

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The purpose of antihypertensive drug therapy is to lower the blood pressure safely and within the limits of tolerable side-effects. This attainment, however, requires a technique which is even more specialized than our present-day methods for controlling diabetes. The technique is based on the following principles.

Technique of Antihypertensive Drug Therapy

1. *Individual Differences.*—Some patients will respond best to one type of antihypertensive agent, others to another. In addition, the dosage requirement may differ markedly from one patient to another. The duration of the blood pressure control also is variable, some patients requiring one or two doses per day, others three or four.

Patients show marked differences in the incidence and severity of side-effects. There also is a difference in the ability of various patients to tolerate side-effects. Minor discomforts which will be treated as of no consequence by a stoical patient may assume disabling proportions in a more sensitive person.

Some patients are unsuited to antihypertensive drug therapy. In general, aged or prematurely arteriosclerotic persons do not function well when their pressures are reduced. Hypertensive patients in terminal uremia with B.U.N. or N.P.N. elevations above 100 mg. per 100 cc. often will die more rapidly when their blood pressures are lowered. Finally, psychopathic personalities, alcoholics, and severe neurotics often are unable to adhere to a long-term drug treatment program.

2. *Titration.*—Because of the marked differences in responsiveness among individual patients, it is apparent that the dosage needs to be adjusted in each case according to that person's requirement. It is obvious that continued elevation of dosages is permissible only if the drug used is relatively safe. In the past we have regarded the potent ganglionic blocking agents and veratrum derivatives as "dangerous" drugs, whereas we considered the Rauwolfia alkaloids and hydralazine to be relatively innocuous. However, no deaths or true chronic toxic reactions have been reported from either the ganglionic blocking agent, pentolinium (Ansolysen) tartrate, or the veratrum alkaloids. The same cannot be said for hydralazine (Apresoline), which has produced hypersensitivity reactions including a syndrome resembling disseminated lupus erythematosus.* Rauwolfia or reserpine frequently have precipitated severe depressions [3] which probably have led to more deaths because of suicides than any other hypotensive agent. It is important to distinguish between troublesome side-effects and dangerous reactions.

Because of the potential and insidious dangers of Rauwolfia and hydralazine and because, in our experience at least, these

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* References 1 and 2.

dangers are increased with large maintenance dosage, we have arbitrarily decided on a maintenance dose of 0.25 mg. of reserpine daily and a ceiling of 200 mg. of hydralazine daily. With pentolinium tartrate and the veratrum alkaloids, however, the dosages are elevated until there is either a reduction of blood pressure or disturbing side-effects.

3. *Blood Pressure Control.*—Experience has shown that the level of blood pressure in most hypertensive patients is subject to considerable fluctuations, particularly when under treatment. Many patients will exhibit marked elevations of blood pressure when they visit the doctor's office.[4] It is apparent that if dosages of potent antihypertensive drugs are regulated on the basis of these falsely high pressures side-effects and collapse reactions resulting from overmedication will be frequent. Reliance on occasional office recordings as a guide to dosage regulation probably is the main reason for failure to obtain satisfactory results from the ganglionic blocking drugs.

In addition to elevations of blood pressure induced by anxiety, there also are seasonal and diurnal fluctuations.[5] In general, patients are more resistant to hypotentive drugs in cold than in warm weather. The dosage requirement of a ganglionic blocking agent during the winter may be double that required in the summer. The ganglionic blocking drugs also are most effective in the morning and become progressively less so as the day wears on. It is not at all infrequent to find that the afternoon dose of a blocking agent must be two or three times the morning requirement in order to maintain a 24-hour control of blood pressure.

A satisfactory solution to this problem has been the utilization of home blood pressure recordings. The blood pressure usually is recorded before the morning dose of medications, when the patient returns home from work, and at bedtime. A record is kept of these readings, which the physician uses as his guide to dosage adjustment.

Home pressure recordings serve other useful functions. If low pressures are obtained, the patient will call in and often avert major hypotensive episodes. In addition, the patient sees for himself the beneficial results of treatment and will be more willing to tolerate minor side-effects. Finally, the interpretation of symptoms can be made with greater precision, since one can determine whether they were associated with abnormally high or low pressures.

4. *Patient Education.*—The philosophy of modern antihypertensive drug therapy is entirely different from the school which preceded it. In the older philosophy, which might be termed the "coy school" of therapy, every effort was made to "play down" the significance of the hypertension. Since effective methods for reducing blood pressure were not available, the doctor was forced to do the best he could by allaying the emotional factors. If nothing could be done to prevent the progression of the disease, at least the physician could try to keep his patient happy. The patient was told "not to worry" about his hypertension.

The modern school utilizes a more positive approach. The patient becomes an active participant in a program designed to control the hypertension. He is placed in the same situation as the insulin-treated diabetic who is made an active partner in the aims and methods of management.

Backed up by more potent weapons to lower blood pressure, the physician can determine first whether such a need exists. It is not at all uncommon, particularly in agitated middle-aged women, to obtain a history of long-standing marked elevations of blood pressure. Yet, there are little or no signs of organic damage. Home pressure recordings often reveal normotensive or nearly normotensive levels. These patients are not hypertensive except under rare conditions of stress. It would be foolish to treat them with hypotensive drugs. In this instance, home recordings, by revealing to the patient the absence of sustained hypertension, promote more mental comfort than

any verbal reassurance the physician can provide. If, however, the blood pressure is found to be dangerously elevated, positive steps can be taken to reduce it.

It is helpful also to forewarn the patient concerning the possible development of side-effects. He should be told to sit on the edge of the bed for a minute before arising in order to test for postural faintness. Certain of the side-effects, particularly constipation, should be discussed as well as methods of combatting them. At the same time the patient can be comforted by explaining to him that he can eat a normal diet with only modest salt restriction, that he can drink coffee or tea, that he can enjoy a cocktail before dinner (since this usually enhances the hypotensive effects of medication), and that he can be active to within the limits of his physical fitness, since the blocking agents prevent the rise of blood pressure which may occur with exercise. He also may be told that the side-effects are more annoyances than dangers and usually tend to become less frequent as treatment continues. If the patient knows what to expect, he will not tolerate unduly alarmed when and if the side-effects occur.

5. *Combinations.*—Studies from various clinics including our own have shown that combinations of hypotensive drugs produce a more complete control of blood pressure, a lower dosage requirement of any one agent, and fewer severe side-effects.† Combinations of the ganglionic blocking agents with small maintenance dosages of reserpine or hydralazine or both are particularly effective. Veratrum also usually is better tolerated when combined with small doses of reserpine. In order to keep the maintenance dosages of reserpine and hydralazine within the safest possible range these should be administered in separate tablets and not in single combination tablets.

6. *Adjuncts.*—Adjuncts are used to combat certain side-effects of the ganglionic blocking agents. Constipation is the most frequent side-effect. Some cases can be controlled with prunes or prune juice and laxatives (such as cascara sagrada or magnesium hydroxide) given at bedtime. Some will require in addition neostigmine (Prostigmin) given orally in doses ranging from 15 to 45 mg., the requirement varying in different patients.[5] This is best taken on arising in the morning. If the dose is sufficient, a bowel movement results within an hour. Too large a dose can produce cramps, diarrhea, and nausea.

Another common side-effect is dryness of the mouth due to inhibition of the parasympathetic supply to the salivary glands. The most effective agent in combatting this is pilocarpine nitrate in a dose of 5 to 10 mg. orally taken one-half hour before meals or whenever dryness of the mouth is troublesome.[5] Overdosage may lead to excessive salivation, sweating, and shivering.

Impairment of visual accommodation may occur producing blurred vision for near but not for distant gaze and inability to accomodate to bright light, particularly strong sunlight. An inexpensive pair of "dime-store" reading glasses (which the patient can fit by finding the pair which will make fine print legible) and a pair of dark glasses will take care of this usually temporary problem.

Strangely enough, salt is an important adjunct when the ganglionic agents are employed. A moderate salt intake is all that is required. If salt is rigidly restricted, a dose of the ganglionic blocker insufficient to lower the supine blood pressure will produce disabling postural hypotension. However, salt can and should be sharply restricted in the presence of edema.

Schedules of Treatment

Adjustment Period.—Prior to any treatment in mild or moderate forms of hypertension, the patient is instructed to have his blood pressure recorded at home twice or thrice daily and at such hours that he can carry on his usual occupation. After two weeks of such home recordings, the basal level of blood pressure can be estimated. If it is elevated, treatment may

† References 6-8.

begin with reserpine 0.5 mg. morning and night for two weeks followed by a maintenance dose of 0.25 mg. daily.

If after a two-week trial reserpine alone fails to lower the home pressures, hydralazine may be added, beginning with a dose of 25 mg. four times daily and increasing to 50 mg. per dose if necessary. If this is unsuccessful, hydralazine should be withdrawn but the patient continued on reserpine.

If the home blood pressures still are elevated, and the patient is not markedly arteriosclerotic, uremic, or aged, pentolinium tartrate may be prescribed begining with a dose of 20 mg. after breakfast, at 2 p.m., and at bedtime. The dosages may be raised by 20 mg. increments every two days until the blood pressure falls significantly from its previous levels. It is important that the home pressures be recorded with the patient in the erect position, since dosages should be adjusted on the basis of postural hypotension produced by the ganglionic blocking drugs. Whenever possible during the adjustment period, readings should be taken during the late morning and afternoon as well as the morning and evening recordings.

When the blood pressure falls the patient should be instructed to come to the doctor's office. At that time, any side-effects which might arise can be handled and adjustment of the individual doses during the day carried out so as to provide the least fluctuation of blood pressure during the 24-hour period.

In severe cases, the patient should be hospitalized. Reserpine and a ganglionic blocking agent may be begun simultaneously. Blood pressures should be recorded in both the supine and the erect position by the nursing staff before and two hours after each dose except after the bedtime dose. The dosage of the blocking agent can be raised daily in order to conserve time. If after obtaining a reduction of blood pressure the diastolic still is elevated to 120 mm. of Hg or higher, hydralazine may be added to the treatment regimen. Prior to discharge from the hospital, the patient or a member of his family is taught by the nursing staff to record the blood pressure so that a follow-up of home pressures can be obtained.

Maintenance Phase.—If treatment progresses satisfactorily, the office visits can become increasingly infrequent. Many of our well-adjusted cases are seen only twice per year, usually at the change of the seasons, when dosage readjustment often is necessary. But in the first month the patient should be seen at weekly intervals.

If the blood pressure fluctuates considerably under pentolinium treatment, more uniformity of response often can be obtained by substituting mecamylamine (Inversine). This is the only available ganglionic blocking agent which is completely absorbed from the gastrointestinal tract. As a result, mecamylamine produces a more uniform response from day to day, although certain side-effects, particularly constipation, dryness of the mouth, and difficult micturition, may be more prominent.

If the patient's principal difficulty is persistent side-effects of constipation and dry mouth, it is worth while to substitute chlorisondamine (Ecolid). Aside from the common occurrence of impaired visual accomodation, this ganglionic blocking agent seems to produce less severe side-effects than the other drugs. It is very potent, the average effective dose being approximately half that of pentolinium, but considerably greater than that of mecamylamine.

The severe cases may develop tolerance to any of the blocking agents. If elevation of dosage does not control the situation, it is often helpful to switch to one of the other blocking drugs. Finally, every physician who prescribes reserpine or any Rauwolfia preparation is obligated to warn his patients concerning the possible development of a depression in order to minimize the danger of suicide.

We have entered a new phase in the treatment of hypertension with the development

of drugs that "really do things." This has brought with it a radical revision of attitudes and opinions about the management of the hypertensive patient. The physician's responsibility toward his patients has increased enormously. If he decides to utilize these newer forms of therapy he is obligated to determine the true need in each case and also to administer them in such a way as to obtain maximum effectiveness with minimum risk.

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Adrenal-Regeneration Hypertension and Factors Influencing Its Development

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The role of the adrenal cortex in the pathogenesis of hypertensive cardiovascular-renal disease has long been the subject of scientific debate. However, as a result of recent observations on the therapeutic effect of bilateral adrenalectomy in a small number of hypertensive patients,* the presence of increased quantities of aldosterone in the urine of patients with essential hypertension,† and the production of experimental hypertension with aldosterone,‡ the question no longer seems to be whether or not the adrenal cortex participates in the genesis of certain forms of this disease but rather how the adrenal cortex participates. That it is probably not through a simple "derailment" of the response to nonspecific stress, as originally proposed by Selye,[9] has been shown by the observation that, with the single exception of cold, nonspecific stress has been notably unsuccessful in reproducing hypertension and vascular lesions in the experimental animal.[10] The complexity of adrenal cortical participation has been further emphasized by the fact that corticotropin (ACTH) has failed to produce either hypertension or vascular changes, while both have been produced by growth hormone administration but only in the presence of the adrenal cortex.[11]

The primary importance of some functional aberration of the adrenal cortex in the genesis of hypertensive vascular disease has received further support from the recent observation[12] that hypertension frequently accompanied by necrotizing vascular lesions developed following unilateral adrenalectomy and contralateral adrenal enucleation in uninephrectomized, immature rats given 1% sodium chloride to drink. Since the only difference between the adrenal-enucleated rats which became hypertensive and control animals which did not was the presence of a regenerating adrenal gland, and as the rise in blood pressure occurred during the regeneration of the adrenal cortex from the capsule and adherent cortical cells which remain in situ following the operative procedure, it has been termed "adrenal-regeneration hypertension."[13]

The acquisition of this new technique for the production of experimental hypertension has provided an excellent opportunity for the study of the interplay between the endocrine, electrolyte, and metabolic factors which contribute to its pathogenesis. In embarking upon such a program it seemed reasonable to begin with a study of the importance of those factors which constituted part of the original experimental procedure. Thus the experiments reported in this communication were performed in

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* References 1-4.

† References 5 and 6.

‡ References 7 and 8.

order to obtain answers to the following questions: (1) Is the presence of regenerating adrenal cortical tissue essential? (2) Is it necessary to reduce renal mass? (3) Is it necessary to provide excess available sodium chloride? (4) Is the use of female rats necessary for the development of adrenal-regeneration hypertension?

Materials and Methods

In the first experiment 24 female Sprague-Dawley rats averaging 92 gm. in body weight were divided into two groups of 12 rats each, and 36 hypophysectomized female Sprague-Dawley rats averaging 77 gm. in body weight were divided into two groups of 18 each and treated according to the outline contained in Table 1. The duration of this experiment was seven weeks. In the second experiment 70 female Sprague-Dawley rats averaging 59 gm. in body weight were divided into seven groups of 10 rats each and treated as shown in Table 1. The duration of this experiment was nine weeks. In the third experiment 40 female Sprague-Dawley rats averaging 52 gm. in body weight were divided into four groups of 10 rats each, and 40 male Sprague-Dawley rats averaging 52 gm. in body weight were divided into four groups of 10 rats each and treated as outlined in Table 1. This experiment lasted eight weeks.

Adrenal enucleation was performed by the method of Ingle and Higgins.[14] All rats were fed Purina Laboratory Chow, and sodium chloride was given as a 1% solution to drink ad libitum. Systolic blood pressure was measured by the microphonic manometer method of Friedman and Freed,[15] and the body weight of each rat was determined at the beginning of the experiment and weekly thereafter. Consumption of 1% sodium chloride was calculated for each rat at weekly intervals and expressed for each group as the average 24-hour intake per rat. At the end of each experiment the rats were killed by exsanguination, and the organs to be studied were immediately removed, weighed fresh on a gramatic balance, and fixed in Kenker-formol. In rats with two adrenals one gland was fixed in Zenker-formol and the other in 10% formalin, while in animals with regenerated adrenals the gland was cut in half and one-half fixed in Zenker-formol

TABLE 1

EXPERIMENTAL ARRANGEMENTS

EXPERIMENT 1:

GROUP I:	Right Nephrectomy + NaCl
GROUP II:	Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP III:	Hypophysectomy + Right Nephrectomy + NaCl
GROUP IV:	Hypophysectomy + Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl

EXPERIMENT 2:

GROUP I:	Intact + NaCl
GROUP II:	Right Nephrectomy + NaCl
GROUP III:	Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP IV:	Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP V:	Right Nephrectomy + Left Adrenal-Enucleation + NaCl
GROUP VI:	Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + Water
GROUP VII:	Right Nephrectomy + Water

EXPERIMENT 3.

GROUP I:	Female + Right Nephrectomy + NaCl
GROUP II:	Male + Right Nephrectomy + NaCl
GROUP III:	Female + Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP IV:	Male + Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP V:	Castrate Female + Right Nephrectomy + NaCl
GROUP VI:	Castrate Male + Right Nephrectomy + NaCl
GROUP VII:	Castrate Female + Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl
GROUP VIII:	Castrate Male + Right Nephrectomy + Right Adrenalectomy + Left Adrenal-Enucleation + NaCl

and the other half in 10% formalin. Paraffin sections were prepared from all tissues and stained with hematoxylin and eosin. Frozen sections of the formalin-fixed adrenals were cut at 8μ and stained with Sudan IV, using a hematoxylin counterstain.

Results

Experiment 1

Influence of Hypophysectomy.—During the experiment two rats in Group III and four rats in Group IV died and were discarded. In Figure 1 the growth of the rats in Groups I and II is seen to have been satisfactory, while the growth of the hypophysectomized animals (Groups III and IV) was negligible. In general the sodium chloride intake of the hypophysectomized animals (Groups III and IV) was slightly less than that of the rats in Groups I and II, but it should be noted that the difference was significant only at the third and fourth weeks of the experiment. In the lower part of the figure it can be seen that the systolic blood pressure of the rats of Group II began to rise during the second week and reached a terminal maximum of 170 mm. of Hg. In contrast, the blood pressure of both groups of hypophysectomized animals de-

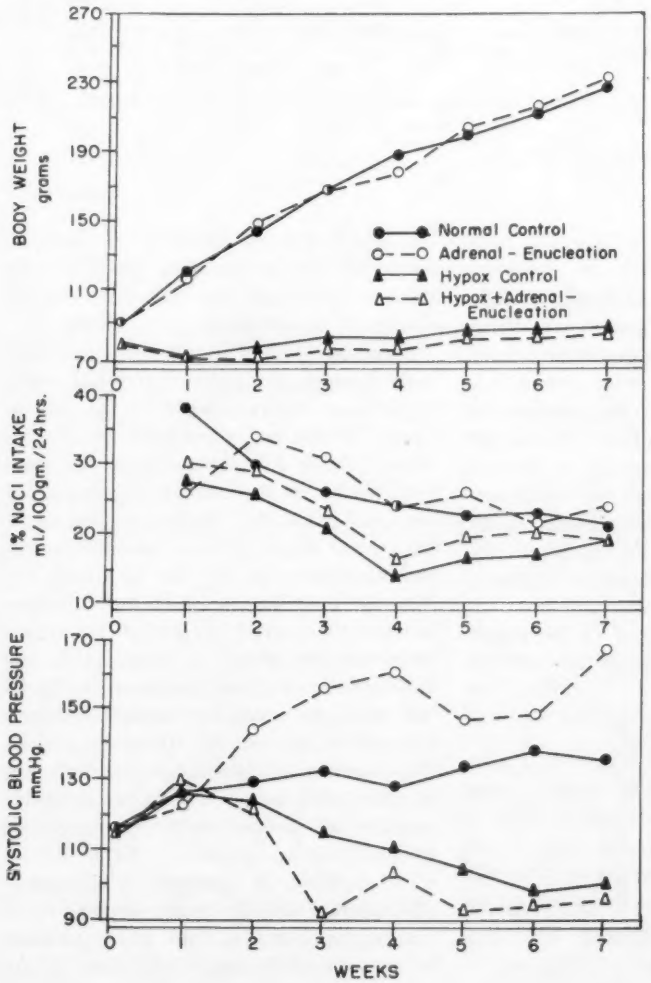

Fig. 1.—Influence of hypophysectomy on the development of adrenal-regeneration hypertension.

creased during the experiment and terminally averaged 96 mm. of Hg in Group IV. Thus, hypophysectomy completely prevented the development of "adrenal-regeneration hypertension".

In Table 2 are shown the organ weights expressed as milligrams per 100 gm. of body weight. Commensurate with the hypertension of the rats of Group II there was slight but significant cardiac and renal hypertrophy. In view of the modest hypertension and cardiac hypertrophy in this group, it is noteworthy, perhaps, that the regeneration of the enucleated gland in these rats was not as great as had been observed in previous experiments.§ There were no differences between the average organ weights of the rats in Groups III and IV except for the adrenal gland, where inhibition of regeneration was evident in the latter animals.

No lesions were observed in the organs examined from the rats of any of the groups.

TABLE 2.—*Influence of Hypophysectomy on the Organ Weights of Rats with Adrenal-Regeneration Hypertension*

Group	No. of Rats	Organ Weights, Mg./100 Gm. Body Weight							
		Heart	Kidney	Adrenal(s)	Brain	Liver	Thymus	Spleen	Pituitary
I	12	328 ± 17*	568 ± 15	28.0 ± 0.7	765 ± 12	3400 ± 175	165 ± 7	232 ± 11	4.8 ± 0.1
II	12	375 ± 8	657 ± 13	16.0 ± 0.14	759 ± 12	3871 ± 114	172 ± 9	247 ± 10	4.8 ± 0.3
III	16	344 ± 6	453 ± 8	9.2 ± 0.3	1851 ± 26	3345 ± 45	140 ± 7	144 ± 5	
IV	14	346 ± 5	453 ± 5	1.6 ± 0.13	1940 ± 22	3547 ± 48	157 ± 6	153 ± 3	

* Standard error of the mean.

Experiment 2

(a) Influence of Renal Mass.—In Figure 2 the average weekly body weight, saline consumption, and systolic blood pressure of the rats in Groups I, II, III, and IV are plotted. There was no significant difference in the average growth or saline consumption of the four groups. On the other hand, it is apparent in the lower part of the Figure that the blood pressure of the rats in Group III rose rapidly during the first five weeks and remained at highly significant hypertensive levels for the terminal four weeks of the experiment. In contrast, the rats of Group IV, which differed from the animals of Group III only in that they possessed both kidneys instead of one, failed to develop significant hypertension.

Significant cardiac hypertrophy developed in the hypertensive rats of Group III, while the average cardiac weight of the rats in Group IV did not differ from the control values (Table 3). Furthermore, the renal hypertrophy in the animals of Group III was such that the weight of the single kidney was slightly greater than the weight of both kidneys in the rats of Group IV. Although there was no significant difference between the average weight of the regenerated adrenal glands in Groups III and IV, the values for both groups were slightly less than the combined weight of both adrenals in the rats of Groups I and II. The presence of splenic and pituitary enlargement and thymic atrophy in Group III are also in contrast with the changes of Group IV.

(b) Influence of Contralateral Adrenal.—The average weekly body weight, saline consumption, and systolic blood pressure of the rats of Groups II, III, and V are

§ References 12, 13, and 16.

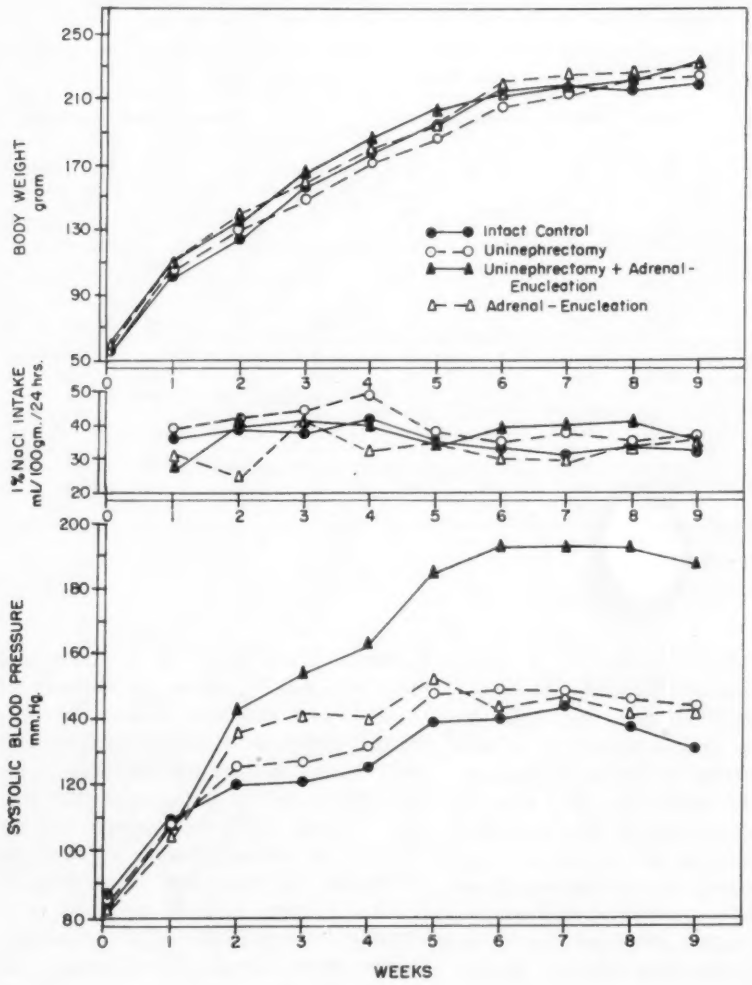

Fig. 2.—Influence of renal mass on the development of adrenal-regeneration hypertension.

shown in Figure 3. The growth curves of all groups were the same. Similarly, there was no significant difference in saline consumption between any of the groups. On the other hand, significant hypertension occurred in the rats in Group III, while no elevation of systolic blood pressure above control levels developed in the rats of Group V.

In agreement with the observations on blood pressure, Table 3 shows that neither cardiac nor renal hypertrophy was present in the rats of Group V, in contrast to the marked hypertrophy of these organs in the hypertensive rats of Group III. In addition, the combined weight of the right adrenal and unregenerated remnant of the enucleated left adrenal in the rats of Group V did not differ from the weight of the regenerated adrenal in the rats of Group III. It should also be noted that the right adrenal gland in the rats of Group V had undergone compensatory hypertrophy, since it was larger than either of the adrenal

TABLE 3.—*Influence of Renal Mass, Contralateral Adrenal, and Sodium Chloride on the Organ Weights of Rats with Adrenal-Regeneration Hypertension*

Group	No. of Rats	Organ Weights. Mg./100 Gm. Body Weight							
		Heart	Kidney(s)	Adrenal(s)	Brain	Liver	Thymus	Spleen	Pituitary
I	10	365 ± 7*	870 ± 17	29.7 ± 1.4	748 ± 21	3524 ± 97	143 ± 7	239 ± 9	4.6 ± 0.6
II	10	383 ± 7	767 ± 31	30.8 ± 0.7	753 ± 16	3560 ± 117	126 ± 7	272 ± 4	4.6 ± 0.1
III	8	494 ± 30	971 ± 51	24.7 ± 3.0	842 ± 83	4200 ± 300	125 ± 15	347 ± 30	5.2 ± 0.14
IV	9	390 ± 13	944 ± 22	21.1 ± 0.7	747 ± 13	3720 ± 117	126 ± 5	269 ± 16	4.4 ± 0.1
V	8	366 ± 6	732 ± 15	21.4 ± 0.7	774 ± 20	3807 ± 123	159 ± 9	264 ± 8	4.4 ± 0.2
VI	10	358 ± 8	749 ± 50	20.9 ± 1.1	770 ± 17	3650 ± 103	139 ± 8	297 ± 11	4.7 ± 0.1
VII	10	337 ± 11	598 ± 12	29.0 ± 1.3	743 ± 16	3147 ± 87	149 ± 8	293 ± 8	4.5 ± 0.17

* Standard error of the mean.

glands in the rats of Group II.

(c) Influence of Sodium Chloride.—Figure 4 shows that there was again no difference in the growth rate of the animals under consideration. It also shows that the consumption of water by the adrenal-enucleated rats of Group VI was much less than the consumption of 1% sodium chloride by the similarly operated-on animals of Group III. It is noteworthy, furthermore, that the substitution of water for saline drinking fluid completely inhibited the development of hypertension in animals bearing regenerated adrenals (Group VI), while those allowed to drink saline developed significant hypertension.

As shown in Table 3, there was also complete inhibition of cardiac and renal hypertrophy in the rats of Group VI, as compared to Group III. The weight of the regenerated adrenal in the former rats was slightly less than that in the animals of Group III, but the difference was again not significant.

A summary of the morphologic findings is presented in Table 4. It is readily seen that there was significant development of renal, cardiac, and brain lesions and periarteritis nodosa in the animals of Group III and that, just as there was inhibition of the hypertension by the presence of both kidneys (Group IV), the presence of the contralateral adrenal (Group V), and the substitution of water for saline drinking solution (Group VI), so also was there virtually complete inhibition of morphologic changes in the animals of these groups. No significant difference in the morphologic appearance of the regenerated adrenals in Groups III, IV, and VI was observed except for the presence of sclerosis and fibrinoid necrosis of periadrenal arterioles in three of the eight rats in Group III.

Experiment 3

Influence of Sex and Castration.—The average weekly body weight, saline consumption, and systolic blood pressure of the female rats are presented in Figure 5. The greater growth of the castrated animals

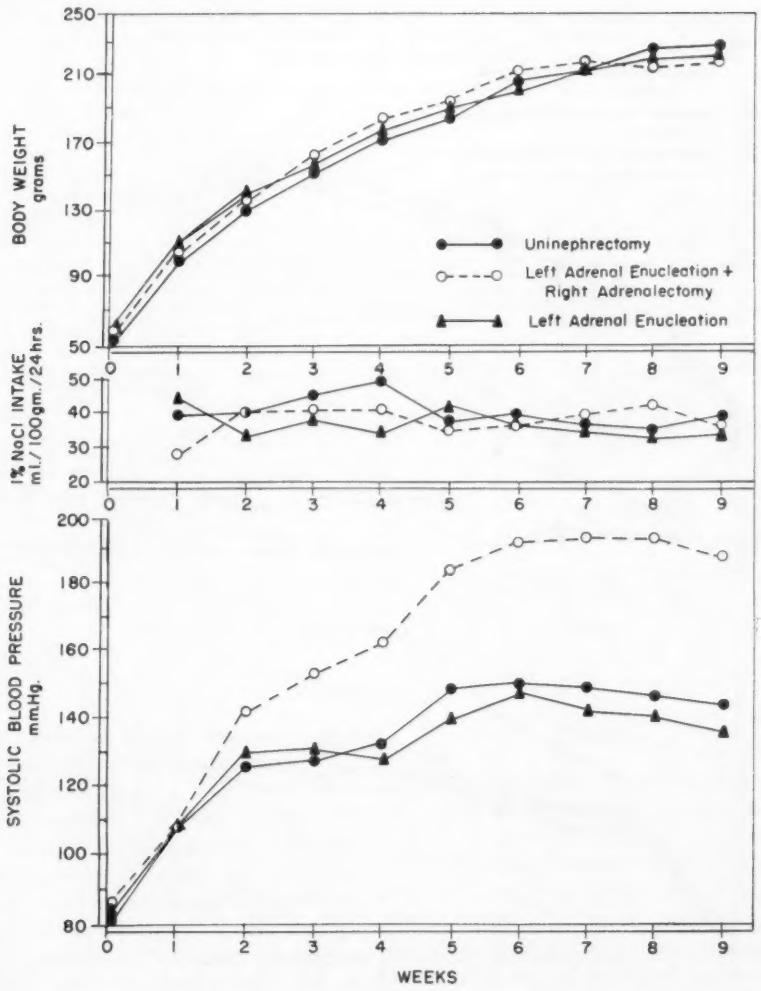

Fig. 3.—Influence of contralateral adrenal on the development of adrenal-regeneration hypertension.

is apparent. Because of the greater growth of these rats, their saline consumption is less than the noncastrated animals when expressed as milliliters per 100 gm. of body weight, although in absolute values the consumption of all four groups was essentially the same. Nonetheless, no polydipsia occurred in either noncastrated or castrated rats with regenerated adrenals, as compared to their appropriate controls, yet both groups became significantly hypertensive. The blood pressure levels of the castrated female animals bearing regenerated adrenals was slightly greater than in the similarly treated noncastrated rats, but the difference was not statistically significant.

The average weekly body weight, saline consumption, and systolic blood pressure of male rats are shown in Figure 6. The growth of the castrated male rats is seen

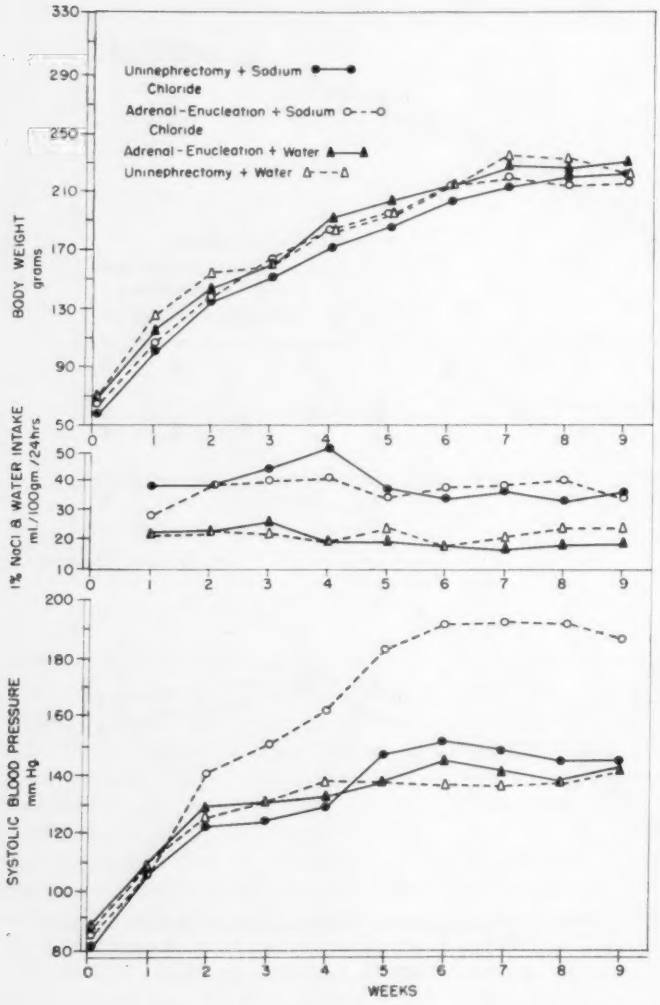

Fig. 4.—Influence of sodium chloride on the development of adrenal-regeneration hypertension.

to have been less than the noncastrated rats, but despite this difference in weight the saline consumption of all groups was essentially the same even when expressed as milliliters per 100 gm. of body weight. Again in the absence of polydipsia both groups of rats bearing regenerated adrenals developed significant hypertension, which was greater but not significantly so in the castrate males.

In Table 5 all groups of hypertensive rats (Groups III, IV, VII, and VIII) are seen to have cardiac hypertrophy which was of a significant degree except in Group IV. Statistically significant renal enlargement was also present in these groups. The adrenal glands in the noncastrated male control animals were approximately one-half the size of the glands in the female noncastrated controls, but in the castrated male and female rats the difference in weight be-

TABLE 4.—*Summary of the Morphologic Changes in Rats with Adrenal-Regeneration Hypertension as Influenced by Renal Mass, Contralateral Adrenal, and Sodium Chloride*

Group	Kidney	Heart	Brain	Pancreas and Mesentery
I	No lesions	No lesions	No lesions	No lesions
II	Slight degeneration of capillaries in a few glomeruli of all rats.	No lesions	No lesions	No lesions
III	Arteriolar nephrosclerosis, fibrinoid necrosis of glomeruli and arterioles, and tubular dilatation with casts; lesions present to some degree in all rats	Focal arteriolar sclerosis and fibrinoid necrosis with perivascular fibroblastic proliferation; lesions present in 4 of 8 rats	Edema, neuronal degeneration, arteriolar sclerosis, and cystic infarcts; lesions present in 2 of 8 rats	Periarteritis nodosa in 3 of 8 rats
IV	Slight degeneration of capillaries in a few glomeruli of all rats	No lesions	No lesions	No lesions
V	Slight degeneration of capillaries in a few glomeruli of all rats	No lesions	No lesions	No lesions
VI	Slight degeneration of capillaries in a few glomeruli of all rats; one rat showed slight arteriolar nephrosclerosis	No lesions	No lesions	No lesions
VII	No lesions	No lesions	No lesions	No lesions

tween the adrenal glands was much less. Furthermore, the weight of the regenerated adrenal gland relative to body weight was significantly greater in the noncastrated female animals than it was in the castrated female rats, while there was no significant difference between the weight of the regenerated adrenal in the castrated male animals and the noncastrated male rats. Also the thymus was not significantly atrophic in any of the hypertensive groups, and the spleen was uniformly larger than the controls.

The morphologic changes in the various groups of hypertensive rats of this experiment were decreased in both incidence and severity as compared with most previous experiments. However, careful histologic study has shown that there was no apparent difference in either incidence or severity of lesions between the castrated and noncastrated female rats, while castrated males seemed to have both a slightly greater incidence and severity of lesions than did noncastrated males.

Comment

The occurrence of arterial hypertension in adrenal-enucleated uninephrectomized rats given 1% sodium chloride to drink and the presence of vascular lesions in many of the hypertensive rats of the second and third experiments again confirms similar previous observations.|| However, the absence of lesions in the hypertensive rats of the first experiment and their low incidence and decreased severity in the hypertensive animals of the third experiment suggests that the pathogenesis of the vascular changes involves factors other than the simple elevation of blood pressure. Indeed, recent studies have indicated that the age factor alone is important in the development of both hypertension and vascular lesions, since it has been shown that immature female rats develop adrenal-regeneration hypertension with vascular lesions, while young mature animals do not.[16] As yet

|| References 12, 13, and 16.

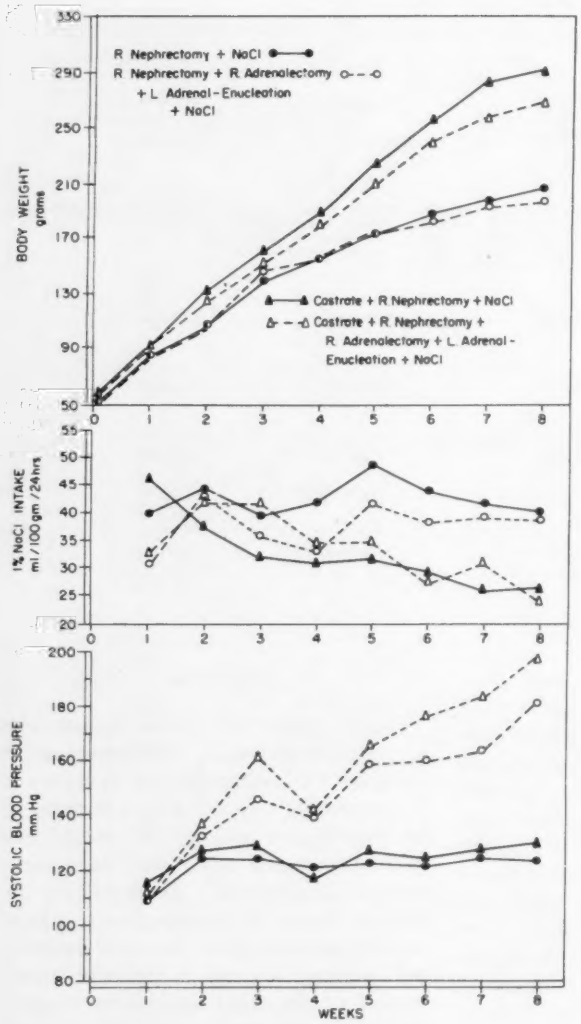
R Nephrectomy + NaCl
R Nephrectomy + R Adrenalectomy
+ L Adrenal - Enucleation
+ NaCl
Castrate + R Nephrectomy + NaCl
Castrate + R Nephrectomy +
R Adrenalectomy + L Adrenal -
Enucleation + NaCl
BODY WEIGHT grams
1% NaCl INTAKE ml / 100 gm / 24 hrs
SYSTOLIC BLOOD PRESSURE mm Hg
WEEKS

Fig. 5.—Influence of sex and castration on the development of adrenal-regeneration hypertension in female rats.

there is no explanation for this effect of age, but it has been speculated that it may be related to some quantitative or qualitative difference in secretory capacity of the regenerating adrenal cortex in immature and mature rats, to the difference in saline consumption which exists between immature and mature animals, or to a greater tissue susceptibility in immature rats as a result of their greater secretion of growth hormone.

The significance of several additional factors in the genesis of adrenal-regeneration hypertension and vascular disease has been studied in the present experiments. In the first and second experiment the essentiality of regenerating adrenal cortical tissue

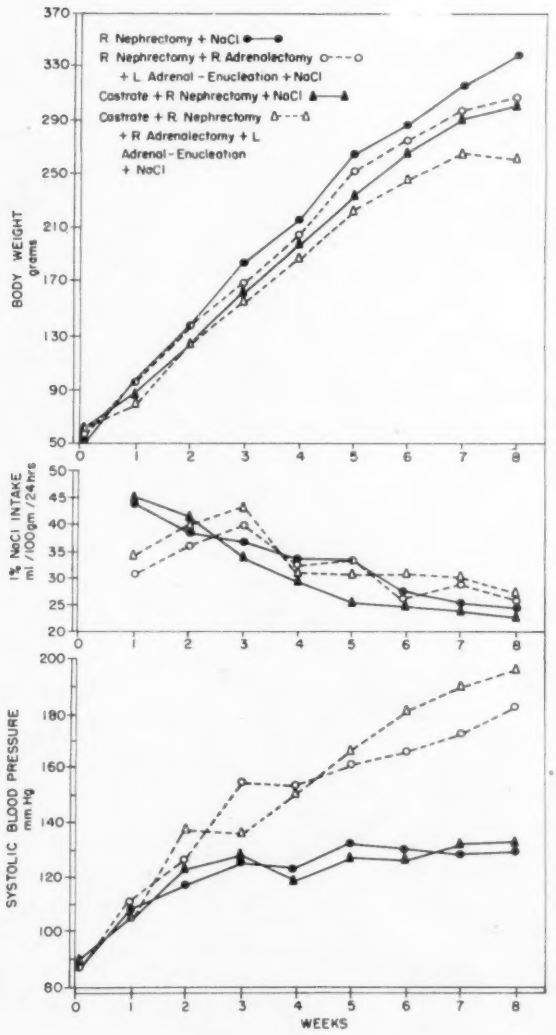
R. Nephrectomy + NaCl
R. Nephrectomy + R. Adrenalectomy + L. Adrenal - Enucleation + NaCl
Castrate + R. Nephrectomy + NaCl
Castrate + R. Nephrectomy + R. Adrenalectomy + L. Adrenal - Enucleation + NaCl
BODY WEIGHT grams
1% NaCl INTAKE ml./100gm./24hrs.
SYSTOLIC BLOOD PRESSURE mm.Hg
WEEKS

Fig. 6.—Influence of sex and castration on the development of adrenal-regeneration hypertension in male rats.

has been shown, since inhibition of adrenal regeneration either by hypophysectomy or by the presence of the contralateral intact adrenal gland was accompanied by failure of hypertension and vascular lesions to develop. The unique as well as essential qualities of regenerating cortical tissue in the genesis of this hypertensive disease is demonstrated in the second experiment, where, even though the intact contralateral adrenal underwent compensatory hypertrophy, no hypertension or vascular lesions were produced.

According to Selye and Pentz,[17] uninephrectomy merely serves to sensitize the rat to the hypertensive and vasculotoxic effects of desoxycorticosterone acetate (DCA), but the results of the present experiments indi-

TABLE 5.—*Influence of Sex and Castration on the Organ Weights of Rats with Adrenal-Regeneration Hypertension*

Group	No. of Rats	Organ Weights, Mg./100 Gm. Body Weight											
		Heart	Kidney	Adrenal(s)	Brain	Liver	Thymus	Spleen	Pituitary	Ovaries	Uterus	Testes	Seminal Vesicles
I	7	379 ± 4*	696 ± 35	31.2 ± 0.9	817 ± 16	3876 ± 185	170 ± 12	299 ± 23	4.6 ± 0.14	40 ± 2	220 ± 40	--	--
II	9	328 ± 8	666 ± 21	15.2 ± 0.5	522 ± 11	3329 ± 94	155 ± 10	218 ± 13	2.9 ± 0.1	--	--	1010 ± 25	235 ± 11
III	10	492 ± 36	927 ± 79	23.9 ± 2.8	902 ± 48	4408 ± 433	156 ± 11	384 ± 49	4.5 ± 0.11	35 ± 2	253 ± 31	--	--
IV	9	388 ± 28	810 ± 38	9.4 ± 0.8	594 ± 38	4389 ± 195	149 ± 8	233 ± 15	3.0 ± 0.1	--	--	1036 ± 55	263 ± 9
V	9	331 ± 10	608 ± 16	28.6 ± 1.1	623 ± 8	3091 ± 147	307 ± 21	254 ± 9	4.1 ± 0.2	--	21.5 ± 0.8	--	--
VI	9	333 ± 8	621 ± 24	23.8 ± 1.1	585 ± 8	3100 ± 150	290 ± 5	242 ± 8	4.4 ± 0.1	--	--	--	3.1 ± 0.15
VII	9	438 ± 17	748 ± 24	14.5 ± 1.1	672 ± 44	4261 ± 195	289 ± 24	338 ± 32	4.4 ± 0.17	--	32.5 ± 1.4	--	--
VIII	10	470 ± 52	850 ± 93	12.8 ± 1.3	711 ± 45	4305 ± 492	216 ± 23	347 ± 19	5.3 ± 0.3	--	--	--	3.4 ± 0.2

* Standard error of the mean.

cate that reduction in renal mass is truly essential for the development of adrenal-regeneration hypertension and vascular disease. The mechanism by which reduction of renal mass participates in the genesis of these states is not known, although it must be borne in mind that even in otherwise untreated rats sufficient reduction of renal substance by surgical excision is sufficient to produce experimental hypertension.¶ It is conceivable, therefore, that the kidney serves to inactivate or metabolize some substance, possibly of adrenal cortical origin, which produces hypertension, and in the presence of only one kidney insufficient quantities would be inactivated, and hypertension would be the consequence. Needless to say, the role of the kidney in the genesis of this form of hypertension needs to be clarified.

It is well known [20] that administration of increased amounts of sodium chloride to normal rats for a long time will result in hypertension and vascular lesions similar to those observed under the present experimental conditions of adrenal enucleation. On the other hand, it has been observed in these as well as in previous experiments that hypertensive animals bearing a regenerated adrenal cortex do not consume significantly more saline drinking solution than do control animals which are not hypertensive. Hence, the hypertension and vascular changes which develop during adrenal cortical regeneration cannot be ascribed to increased sodium chloride consumption alone. However, as shown in the second experiment, when sodium chloride drinking solution is no longer available to such animals neither hypertension nor vascular lesions develop. Thus one must conclude that, while it is not essential for animals bearing regenerating adrenals to consume greater quantities of sodium chloride drinking fluid than control animals in order for hypertension and cardiovascular-renal lesions to develop, it is necessary for sodium chloride to be available. This observation serves to substantiate the conclusions of other investigators that sodium chloride plays some as yet unexplained role in the genesis of experimental hypertension in the rat.

Female rats have long been held [21] to be more susceptible to the hypertensive and vasculotoxic actions of DCA than are male rats, and castration tends to decrease the sensitivity of female animals, while increasing the sensitivity of males. Insofar as the present experiments are concerned, the results indicate that adrenal-regeneration hypertension can occur in both male and female rats and that castration has little effect on its development in either sex.

Conclusions

The influence of hypophysectomy, presence of the contralateral adrenal gland, renal mass, sodium chloride, and sex on the development of adrenal-regeneration hypertension has been studied in immature Sprague-Dawley rats. The following conclusions have been drawn:

1. The presence of actively regenerating adrenal cortical tissue is necessary for the development of this form of experimental hypertension and vascular disease, since in those animals in which adrenal regeneration was prevented by hypophysectomy or the presence of the contralateral intact adrenal gland hypertension and vascular lesions were inhibited.

2. Reduction in renal mass is also necessary for the production of hypertension in this procedure, since in animals possessing both kidneys neither hypertension nor vascular lesions occurred.

3. While polydipsia does not usually develop in hypertensive animals bearing regenerated adrenal cortices, it has been shown that available sodium chloride is necessary for the development of this form of experimental hypertension, since replacement of saline drinking solution by tap water completely inhibits its development.

4. Both hypertension and vascular lesions have been shown to develop in castrated and noncastrated rats of either sex, thus indicat-

¶ References 18 and 19.

ing that neither sex nor castration materially influences their development.

Summary

A study has been made to determine the influence of several factors on the development of adrenal-regeneration hypertension and vascular disease. It has been found that hypophysectomy, the presence of the contralateral intact adrenal gland, the presence of both kidneys, or the substitution of water for saline drinking fluid inhibit the development of this hypertensive vascular disease, but neither sex nor castration has any significant effect. It is concluded that in order for this form of experimental hypertensive vascular disease to develop there must be actively regenerating adrenal cortical tissue, a reduction in renal mass, and availability of excess sodium chloride.

Mr. James Guillebeau and Miss Anne Dye provided technical assistance in the conduct of these experiments, and Miss Betty Wilson provided the histological preparations. The charts were prepared by the Department of Medical Illustration.

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Why Drugs Are Not Enough in the Treatment of Tuberculosis

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With the advent of long-term chemotherapy [6] and the resultant conversion of a large percentage of patients' sputums and gastric cultures, there were many optimistic opinions that the present antituberculous drugs would cure tuberculosis. D'Esopo and coworkers [7] reported that when these patients whose cultures had converted on streptomycin and PAS were resected, it was difficult to grow tubercle bacilli from the resected specimens. However, acid-fast rods were present in a large number of these specimens, so the question arose: Are these tubercle bacilli dead or merely dormant? [11] By six months after chemotherapy was stopped a significant percentage of the negative nonresected patients with open cavities had reactivated.[12] On June 1, 1952, we began our present treatment regimen, consisting of streptomycin, aminosalicylic acid, and isoniazid used concurrently and continuously from admission to discharge, with early resectional surgery when indicated.[1] When digested portions of our first 22 resected specimens after June 1, 1952, were cultured, only one patient had a negative gastric culture before resection and a positive culture from a digested portion of the specimen. The cultures of the other 21 specimens corresponded to the gastric culture before resection. This is an evaluation of results of gastric culture before resection, culture of resected specimens compared with the pathology of the specimens from patients who were operated on either during their first hospital admission or after reactivation.

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Medical Director and Superintendent, Central Washington Tuberculosis Hospital.

Material and Methods

The results of the gastric culture before resection and the culture of a portion of the specimen using caseous and/or cavitary disease are available for analysis in 171 cases (Table 1).

TABLE 1.—*Results of Culture*

26 positive before surgery....	23 positive specimens 3 negative specimens
145 negative before surgery...	18 positive cultures of specimens 16 positive smear but negative culture 111 negative culture of specimen

The tissue is digested for 24 hours in 2% NaOH solution at 37 C then centrifuged at 3300 rpm for 20 minutes; the supernatant fluid is poured off and a part of the sediment is stained by Ziehl-Neelsen's method and is examined by microscopy. The remainder of the sediment is neutralized with HCL and cultured on one tube each of modified Petragnani's and Jansen's modification of Lowenstein's media, then incubated for six weeks, and if no growth is visible at that time it is called negative and is discarded.

An analysis was made of the results of bronchoscopy and pathology of 168 patients, omitting the 3 patients with positive cultures before surgery and negative specimens—this group is too small to be analyzed. Bronchoscopy is necessary because most bronchial stenosis occurs at the point of resection and thus will not appear in the pathology report. In Table 2, the bronchoscopy findings are broken down into stenosis and bronchitis, the pathology into cavitary, caseous, bronchitis, and bronchiectasis. In order to compare the different groups, the diagnoses are broken down into the percentage of the group having this diagnosis, and each diagnosis is listed separately, although usually more than one condition was present in each patient; for example, cavitary and caseous disease. These groups include 23 patients with positive culture before resection and positive culture of resected specimen, 18 with negative culture before surgery and positive culture of resected specimen, 16 with negative culture before surgery and positive smear of resected specimen but negative culture, and 111 with negative culture before surgery and negative culture and smear of resected specimen.

TABLE 2.

	Bronchoscopy		Pathology			
	Stenosis	Bronchitis	Cavitary	Caseous	Bronchitis	Bronchiectasis
Pos. Pos. 23	59%	76%	94%	94%	71%	6%
Neg. Pos. 18	31%	75%	38%	94%	19%	6%
Neg. Pos. smear 16	44%	55%	11%	78%	11%	11%
Neg. Neg. 111	36%	78%	45%	68%	25%	11%
Reactivation 12	25%	50%	43%	50%	36%	7%

Reactivation is a very definite indication that the remaining tubercle bacilli are viable. Since the drugs are most effective the first time they are used, it is my feeling that any patient who has received the average amount of chemotherapy given all of our patients since June of 1952, namely, 194 days of streptomycin, 161 days of PAS, and 185 days of isoniazid, should be resected if reactivation occurs. Cultures and pathology of specimens are available from the 12 patients who reactivated. Of these 12 specimens cultured, 9 had negative gastrics again before resection, 6 of the 9 had positive cultures of resected specimens, and 2 others were positive on smear of the resected specimens. Two patients positive on culture before surgery had positive culture of pathology. The analysis of the findings of bronchoscopy and pathology of all 12 patients is shown on the bottom line of Table 2. The patients with thick-walled cavities having both cavitary and caseous disease are the ones who remain positive in spite of chemotherapy and whose pathology is almost always positive on culture. Those patients with masses of caseous disease may convert readily on gastric or sputum culture, using antituberculous drugs, and yet, when the area is resected, the culture or smear of the resected specimen is frequently positive, and this type of pathology is the commonest one seen in the reactivation group. Caseous disease with a bronchial connection manifest by positive cultures before drug therapy is started is as dangerous a lesion as open cavitation, supporting the works of Auerback and coworkers.[8]

Extrapulmonary disease constitutes the third group of patients demonstrating the ineffectiveness of antituberculous therapy in sterilizing their resected pathology. These include three cases of renal tuberculosis, all of which had negative urine on culture before surgery, yet all three had positive cultures of the urine from the resected kidneys. These patients had received over two months of combined chemotherapy before resection, about half the amount which the pulmonary cases receive before their resections. There are four cases with bone or joint involvement, and three of these had positive cultures of digested portions of bone and cartilage that was removed at the time of exploration. The pathology for all four was positive for tuberculosis. The recovery of tubercle bacilli from six of these seven extrapulmonary lesions seems to indicate that the antituberculous drugs are less effective in sterilizing extrapulmonary lesions than they are in pulmonary lesions.

Comment

There are five characteristics of tuberculosis which make it a particularly difficult disease to treat: first is the tendency of tubercle bacilli to become resistant to any known antibiotic when they can continue to multiply in the presence of small concentrations of the drug [10]; second is the tendency of blood vessels in the diseased area to become obliterated, which in turn further decreases the concentration of drugs where they are most needed [9]; third is the tendency of the disease to produce destruction of tissue known as caseation which has no blood supply and the drugs cannot diffuse into it in sufficient quantity to be bacteriocidal; fourth is the tendency of tubercle bacilli to be present inside of macrophages so any antibotic, such as streptomycin, which does not penetrate the cell membrane is not effective; and fifth is the tendency to obstruct the normal drainage pathways, for example, bronchial stenosis or ureterostenosis. Because of these difficulties, a most careful evaluation of each patient is necessary if the tools we have today in chemotherapy and resection are to give the best results possible. From the analysis of bronchoscopy and pathology, it is impossible to determine which specimens will be posi-

tive on culture. It is also impossible to distinguish between those patients with negative gastrics and negative pathology on culture and those patients who reactivated. It has been our policy to resect pulmonary lesions at the end of three to four months of combined therapy before the emergence of drug-resistant organisms which increase the complications of resection. Resection is done on the basis of what type of pathology is seen in routine anteroposterior tomographs taken after three months of combined chemotherapy, plus the results of bronchoscopy using right-angle and Foroblique telescopes if there is question of endobronchial disease. All bronchial stenosis and bronchiectasis should be resected. All large caseous focci over 2 cm. in diameter and all thick-walled cavities should be resected.

Hobby and co-workers [8] reported on the cultures of pulmonary lesions resected from humans after long-term chemotherapy using a different technique of handling pathological material for culture. The necrotic material was homogenized using a blender instead of NaOH which kills up to 80% of known viable tubercle bacilli; the wash solutions contained albumin, which removes some of the elements toxic to the tubercle bacilli present in caseous disease, avoiding water and saline solutions and incubating the cultures for 9 months instead of 42 days as we have done. They have smeared the material, injected it into guinea pigs, and cultured on many tubes of liquid media and were able to obtain 15 positives from 19 patients, or 78% of their cases. The tubercle bacilli recovered were virulent to guinea pigs, so viable tubercle bacilli are probably present in a larger percentage of our specimens than we have been able to obtain using our present methods. They reported four cases with positive cultures before surgery, and all four had positive cultures of their specimens; thus our 23 positives out of 26 similar cases compares favorably with their results. Another interesting result was that there were 4 retreatment cases, and all 4 were positive on culture of the specimens, where we had 8 out of 12, or 67%.

In this group of 171 patients with pulmonary tuberculosis, 84% converted by the end of four months of combined chemotherapy using all three drugs, a better conversion rate than is possible using streptomycin and PAS. However, of the 145 patients who were negative on culture before surgery, 12% had positive cultures of their specimens, another 11% had positive smears of their specimens, and 11% reactivated, so it is obvious that drugs alone are not enough. Resections have been done on 39% of all patients treated since June, 1952, and our over-all reactivation rate is less than 6%.* This would indicate that with our present techniques and criteria, we are able to determine with a high degree of accuracy those lesions which should be resected, and this decision is reached during the first four months of hospitalization, before resistant tubercle bacilli appear. The presence of tubercle bacilli resistant to one drug increases the probability of postoperative complications, and resistance to both streptomycin and isoniazid makes resection almost prohibitive.[4] In our cases of extrapulmonary tuberculosis, the presence of positive cultures from the pathology of six out of seven cases indicates that chemotherapy of extrapulmonary lesions is less effective in sterilizing these lesions than it is in pulmonary disease.

Conclusions

1. Drug therapy in any combination will not convert all patients.

2. Even though drug therapy may convert gastric and sputum cultures, it is no indication that the lesion is sterile because (*a*) 12% had positive cultures of their specimens; (*b*) 11% had positive smears of their specimens, and (*c*) 11% reactivated.

3. The three-drug combination will convert a larger percentage of patients than any two-drug combination.

4. The types of pathology which are not

* References 2 and 3.

sterilized by chemotherapy are (*a*) thick-walled cavitary disease; (*b*) caseous masses over 2 cm. in diameter, and (*c*) bronchial stenosis and bronchiectasis.

5. Caseous disease with a bronchial connection manifest by positive cultures before drug therapy is started is as dangerous a lesion as open cavitation.

6. Apparently combined chemotherapy is less effective in extrapulmonary tuberculosis than it is in pulmonary disease.

7. Using equipment and techniques available only in a tuberculosis hospital, that is, good culture methods, anteroposterior tomographs, and bronchoscopy using right-angle and Foroblique telescopes, it is possible to determine which patients will require more than combined chemotherapy alone.

8. If resectional surgery is indicated it should be done three to four months after starting combined chemotherapy.

9. The acid-fast rods found in pathology specimens are viable, virulant tubercle bacilli and if not removed surgically will result in reactivation.

10. Drug therapy is merely a tool in the treatment of tuberculosis, effective for a limited time, and if it is not properly used, the patient will have lost the opportunity for successful resection.

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Oral Absorption Tolerance Tests in Tropical Sprue

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Introduction

After the introduction of liver extract by Castle and co-workers,[1] adequate and striking clinical improvement has been observed in nearly all patients with tropical sprue in Puerto Rico. At the present time most patients receive folic acid therapy for control of anemia and gastrointestinal symptoms. The course and response to prolonged treatment has been described by Rodriguez-Molina.[2] His follow-up study of patients treated for 10 years emphasized that a complete remission of the process is not possible. Despite a satisfactory hematological remission, indiscretions in the daily diet with excess fatty, fried, starchy, or sweet foods would accentuate diarrhea. Only 25% of the patients had normal blood values.

Past studies have indicated a megaloblastic macrocytic anemia, steatorrhea, impaired absorption of glucose, and abnormal x-ray patterns of the small bowel in untreated patients with tropical sprue.* The present study was initiated to evaluate the oral absorption of several foodstuffs to determine if progressive improvement of small-bowel function could be correlated with the hematologic response during specific therapy. Patients were studied as groups before and after varying periods of treatment. In a few instances the same patient was studied in each group.

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* References 3 and 4.

Materials and Methods

All patients studied were natives of Puerto Rico in attendance at the Hematology Clinic, Bayamon District Hospital.† Fifty-five patients were studied whose ages varied from 13 to 78 years. Forty per cent of the patients studied were under the age of 50 years; two patients were less than 20 years old. Patients with a clinical history of weight loss, diarrhea, and lassitude associated with glossitis, macrocytic anemia, and a megaloblastic bone marrow were considered to have a diagnosis of untreated tropical sprue. Marked glossitis was not a common observation, although all patients had at least minimal atrophy and redness of the tongue. A careful fecal examination to exclude parasitic or bacterial infestations as an etiology for diarrhea was performed. In some instances x-ray studies of the small-bowel pattern with a barium sulfate meal revealed abnormal segmentation and flocculation as defined by Adlersberg and co-workers.[5] Twelve patients also had duodenal enzyme studies done to exclude pancreatic disease. Normal values for lipase, amylase, and trypsin were present in all patients, and further evaluation was not continued.

All untreated patients were hospitalized for study and observation. Previously treated patients were evaluated in the Hematology Clinic, except in a few instances where hospitalization was required for other procedures. The majority of patients received 5 mg. of oral folic acid daily for control of their macrocytic anemia. Some patients also required oral iron therapy to obtain an adequate hematological remission. Four older patients with achlorhydria received 30γ of vitamin B_{12} intramuscularly weekly instead of folic acid. Treated tropical sprue patients were defined as those who had received at least four months of specific therapy for macrocytic anemia. The majority of patients had been treated for more than one year. A four-month period was selected, since patients had stabilized weight gain and peripheral blood levels after such a period of antianemic

† Dr. M. Paniagua and Dr. D. Santiago-Stevenson cooperated in referring patients for study.

therapy. Most patients had hemoglobin values of 11 to 12 gm. per 100 ml. Although the majority of patients had no further diarrhea after a month of specific therapy, a small group continued to have loose stools for one- or two-day periods intermittently. The treated tropical sprue patients had been hospitalized previously with the criteria listed above for untreated patients.

Patients without macrocytic anemia or gastrointestinal symptoms were studied to evaluate oral tolerance tests and to compare the values with those obtained in sprue patients.‡ All procedures were not done in each case of tropical sprue, for severe anemia and debilitation did not permit postponement of therapy in some instances. In view of the poor reproducibility of the oral glucose tolerance test,[6] the absorption of D-xylose was substituted. Twenty-five grams of this pentose was given orally in 500 ml. of water. A fasting and hourly venous blood samples were collected for a five-hour period. The patient also collected all urine for the same five-hour period. Analysis of blood and urinary xylose was done by the method of Turner and Brien.[7] As the study progressed, the five-hour urine excretion revealed good diagnostic changes, and blood level determinations were discontinued.

Two procedures to evaluate fat absorption were used:

(1) Oral vitamin A tolerance test. A fasting patient received orally 5 ml. of percomorph liver oil (300,000 I. U.). A fasting and three-, five-, and seven-hour samples of clotted venous blood were collected. The patient ate the noon meal after the five-hour sample was obtained to enhance absorption.[8] Later in the study, the three-hour sample was discontinued. Serum levels of vitamin A were measured with the Carr-Price reaction by the method of Consolazio and co-workers.[9] The results were expressed in micrograms (γ) per 100 ml. of serum, with a standard vitamin A alcohol solution as a reference. The procedure was modified only by using 1:2 dichlorethane as an antimony trichloride solvent, inasmuch as the chloroform solvent was not satisfactory in a humid tropical area.[10] Serum carotenoids were measured on all samples to allow correction for the serum vitamin A measurements. A β-carotene reference standard was used.

(2) Butter fat absorption. A butter-fat tolerance test similar to the procedure used to evaluate blood chylomicrons changes was utilized as outlined by Frazer and Stewart.[11] A breakfast meal of 30 gm. of butter, two pieces of toast or six soda crackers, 100 ml. of fruit juice, and one cup of coffee with sugar was fed to the fasting patients. A fasting and five-hourly samples of clotted blood were collected. During the test period patients were kept quiet and were not allowed to smoke. The clotted samples of blood were allowed to retract at room temperature for several hours and then centrifuged at 2000 g for 15 minutes. The fasting serum was used as a blank sample in the Coleman spectrophotometer at 650μ wave length. The optical density in the hourly samples was read and plotted against time. This procedure measures turbidity or particulate fat droplets during fat absorption. The results are comparable to serum chylomicron counts. In our hands this procedure was more reproducible than chylomicron counting.

‡ Dr. Rafael Rodriguez-Molina aided in this work by allowing us to study some patients for these observations.

Results

D-Xylose Tolerance Test.—Forty-two control hospital subjects were studied to evaluate the blood and urine levels of this procedure. The mean curve of blood D-xylose levels is outlined in Figure 1. A

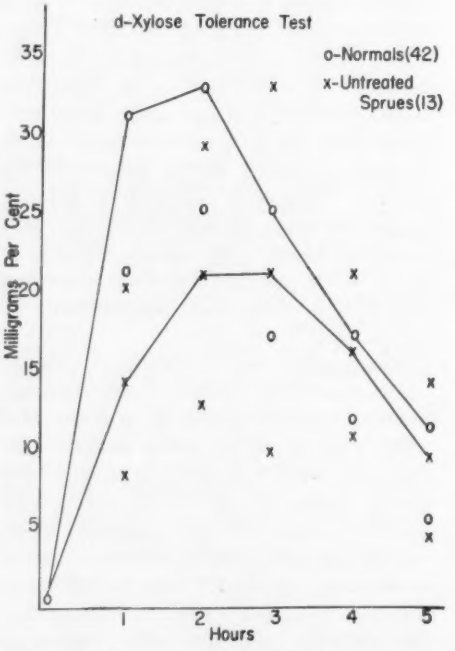

Fig. 1.—Mean curve of blood levels for D-xylose after 25 gm. oral test dose. In this and subsequent charts, figures in parentheses indicate the number of subjects studied. The range of one standard deviation is listed for the normal control subjects and untreated-sprue patients. Only the lower range of the standard deviation is plotted for the normal subjects. Although the blood levels are lower and absorption prolonged in tropical-sprue patients, there is a wide variation in response as reflected in the standard deviation of blood values.

wide range of blood levels was obtained, which is emphasized by the standard deviation (S.D.). These results probably are related to the relationship between a fixed oral dose and variation in body area of the subjects. The mean blood values derived from 13 untreated tropical-sprue patients is outlined for comparison in Figure 1. Blood levels were lower with a prolongation of absorption when compared to the control subjects. In the untreated sprue patients marked variation in the range of the blood levels also existed as noted in the control subjects. Valid detection of impaired absorption of this pentose was not permitted because of the wide overlap between control and sprue-patient blood levels. Blood absorption curves were done also on 21 treated sprue patients. The values were quite similar to those noted in the untreated sprue patients and had the same range of variation. They are not plotted because of the close similarity of the two sprue groups.

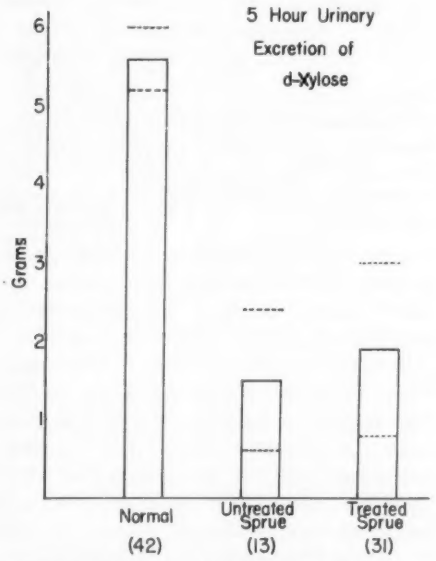

Fig. 2.—The mean five-hour urinary excretion of D-xylose is plotted with one standard deviation, indicated by the dotted lines above and below the bar of the mean values. The test is quite reproducible, with only limited standard deviation in the normal control subjects. Urinary excretion is decreased in the untreated patient and shows only slight improvement during therapy.

In contrast to the blood levels, the five-hour urinary excretion of D-xylose in the control subjects was more reproducible. The controls excreted an average of 5.6 gm. (0.6 gm. S.D.), Figure 2. Thirteen untreated sprue patients had a mean excretion of 1.5 gm. (0.9 gm. S.D.). Thirty-one treated sprue patients had a slightly higher excretion of the pentose, 1.9 gm. (1.1 gm. S.D.). After months or years of therapy

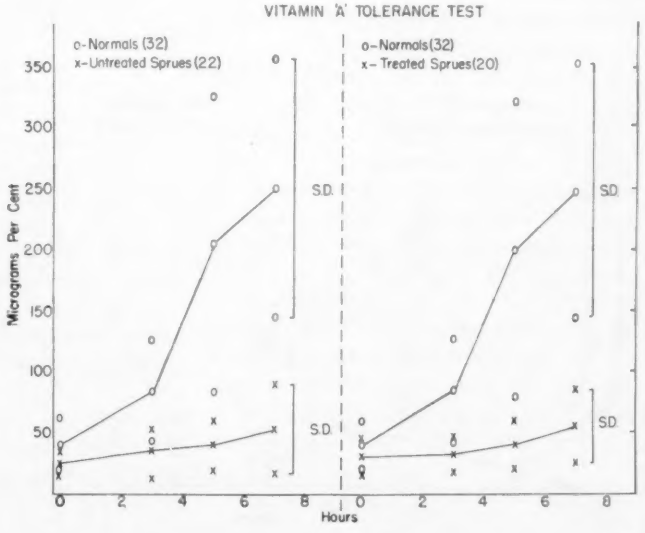

Fig. 3.—Serum levels of vitamin A and the standard deviation (S. D.) at the time intervals listed before and during therapy. The absorption curve is almost identical despite prolonged treatment.

the absorption of this sugar was not improved markedly.

Vitamin A Tolerance Test.—Thirty-two control observations were made, and the results are graphed in Figure 3. As might be anticipated after the oral administration of cod liver oil, there is marked fluctuation in the vitamin A blood values which may be associated with variations in the emptying time of the stomach. At the present time, the three-hour sample has been eliminated, inasmuch as the blood level rise is minimal in this period. There is a progressive rise between five and seven hours. No critical evaluation was made to determine if consumption of the noon meal contributed to the further rise after the seventh hour. A vitamin A serum level of 75γ per 100 ml. or greater at the fifth hour, and a 125γ per 100 ml. level at the seventh hour were considered to be the lower limits of normal vitamin A absorption.

Twenty-two patients with untreated tropical sprue demonstrated poor absorption of vitamin A. There was only a limited elevation of the blood level even at seven hours. It was of interest to observe that an almost identical curve of blood values and standard deviation was noted before or during therapy. In both groups of patients the 5-hour serum level was less than 55γ per 100 ml. when a standard deviation was included.

The fasting mean serum levels of carotenoids and vitamin A were similar in both groups of sprue patients (Table). The

*Fasting Serum Vitamin A and Carotenoid Values**

	No. Patients	Vitamin A, γ/100 Ml.	Carotenoids, γ/100 Ml.
Controls	52	42 (±13)	120 (±57)
Untreated sprue	22	26 (±14)	47 (±53)
Treated sprue	20	29 (±15)	48 (±31)

* The sprue patients during therapy continued to show low values. One standard deviation is listed in parenthesis after each value.

variation in the fasting values of the sprue patients and the control subjects does not allow one to conclude that impaired fat absorption existed from these indices.

Butter-Fat Tolerance Test.—The mean curve of optical density values for 30 control patients is outlined in Figure 4. One may note a wide variation in the standard deviation (S.D.) of the serum value, which probably reflects the variation in stomach emptying time. The usual response to such a standard fat meal is characterized by a peak serum lipemia at the third hour, followed by a marked decline by the fifth hour. An optical density (O.D.) above 0.1 from the second to fourth hour was considered a normal lipemic response to the test meal. Fourteen untreated sprue patients were studied with this butter-fat tolerance test.

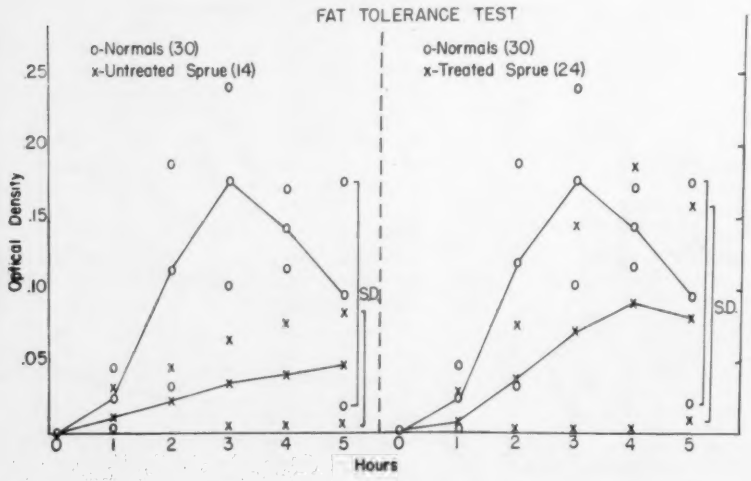

Fig. 4.—Mean serum levels of lipemia are plotted before and during therapy. During treatment improvement of fat absorption is observed. The standard deviation (S. D.) at each time period is marked.

They showed a limited but progressive increase in serum lipemia during the five-hour period. The continuous increase of the lipemic levels without a decline after the third hour appeared to be as important as the measurements of the optical density in any one sample as evidence of delayed absorption.

Twenty-four treated patients with tropical sprue showed higher blood levels. As noted in Figure 4, there is a definite overlap in the standard deviation of this group when compared with the control group. These patients represent all phases of response to treatment and duration of disease. Hence, one would anticipate marked variation in the improvement of absorption. Among these treated patients, five had O.D. values above 0.1 at the third hour; nine had O.D. values above 0.1 at the fourth hour. Hence, there is an improved absorption of fat as measured by lipemia, although 15 (60%) of the patients had a "flat type" of curve similar to that observed in the untreated group. In this small group of treated patients, the persistence of poor fat absorption was not associated necessarily with the older-aged patients.

Comment

All of these patients had a good subjective response to folic acid and/or vitamin B_{12} treatment. Their severe diarrhea, lassitude, and glossitis disappeared. Weight gains were good. A hematological response was obtained, as noted previously by Rodriguez-Molina [2]; hemoglobin values usually stabilized at 11 to 12 gm. per 100 ml. In some instances additional iron therapy was of value. Suarez,[3] in a series of 150 cases, noted that 52% of the patients continued to show macrocytosis after two months of liver-extract therapy. Likewise, some persistence of diarrhea was observed, especially if excess fried, fatty, or starchy foods were used.

The decreased urinary excretion of D-xylose in the untreated sprue patients is similar to results noted in patients with nontropical sprue and among military personnel with malabsorption.§ Brien and co-workers [13] observed among 12 normal subjects an average five-hour urinary excretion of 6.14 gm. Fourman [12] noted an average of 6 gm. among four normal subjects. The present study had a similar five-hour mean value of 5.6 gm. among the 42 control patients studied. This test offers a simple and reliable laboratory method to evaluate small-bowel absorption. Urinary excretion of less than 4 gm. in the five-hour test would warrant further investigation. For reproducible results the urine volume should exceed 150 ml. If renal disease is present or suspected, the blood level of D-xylose two hours after ingestion should be determined for proper interpretation of the urinary values. Low urinary values with a two-hour blood level of 25 mg. per 100 ml. or less tends to eliminate renal disease as a factor. Low urinary values with the two-hour blood level above 50 mg. per 100 ml. may suggest impaired renal excretion.

The mechanism of D-xylose absorption in the bowel is not clear. Brien and coworkers [13] have observed a decline in the plasma inorganic phosphate levels following ingestion of this pentose. In studies of oral glucose absorption, the decline of plasma inorganic phosphate has been attributed to the entry of glucose in body tissues. Fourman || has suggested that the decline of inorganic phosphate indicates active absorption of a sugar. One may therefore suspect that the absorption of D-xylose is associated with an active metabolic process rather than diffusion. Approximately 19 gm. of sugar is not accounted for in this test procedure during the five-hour period. Longer periods of collection do not add perceptible amounts to the urinary excretion. The amount of unabsorbed xylose in the bowel is not known. The rapid decline in blood levels from the third to fifth hours does not distinguish between metabolism of the sugar or termination of absorption. Hele,[16] in rat studies, has demonstrated phosphorylation

§ References 12 and 16.

|| References 14 and 15.

of D-xylose in absorption by the small bowel. These results would also indicate that this pentose is absorbed by an active enzymatic function (xylokinase) of the mucosa.

Only a few previous observations have been made with D-xylose oral absorption during therapy. Fourman [12] saw no significant change in urinary values in tropical-sprue patients receiving liver extract and yeast for periods ranging from 14 days to 2 months. These short-time intervals do not exclude a return to normal absorption of the sugar, for previous observations in nonanemic tropical-sprue patients among military personnel have demonstrated a return to normal urinary excretion values after folic acid therapy.[6] The present study of sprue patients receiving treatment for a minimum of four months, and in the majority of patients for over a year, showed continued low urinary values that were only slightly better than the D-xylose excretion in the untreated disease. The continued marked impairment of D-xylose excretion suggests a permanent defect in small-bowel function, despite the adequate vitamin therapy to revert the megaloblastic bone marrow to a normal cytological pattern.

The oral absorptions of butter fat and vitamin A were decreased in all of the untreated patients. Although the mean values for butter-fat absorption improved after treatment, approximately 60% of the treated patients had a "flat" curve similar to the values noted before therapy. These changes suggest that butter-fat absorption may be a criterion of early improvement of bowel function. Although the group of patients is small, the younger-aged sprue patients did not show a better improvement of butter-fat absorption with therapy. Rather, the treatment of the disease early in its course and the absence of frequent relapses were associated with return to normal lipemic curves. Such observations would correlate well with improvement noted in nonanemic military patients in which the disease had been present for less than a year before treatment was instituted. The persistent poor absorption of vitamin A does not correlate well with the partial improvement noted with butter fat. Legerton and co-workers [17] has emphasized the value of vitamin A absorption as an index of fat absorption. Previous studies among military personnel have emphasized that no good comparison could be made between oral vitamin A absorption and daily fecal fat excretion.[6] Measurements of blood levels of butter fat and vitamin A reflect primarily the rate of absorption, especially of the upper portion of the small bowel. The low blood levels observed before and during therapy do not necessarily reflect the degree of steatorrhea. As noted in the butter-fat-absorption mean curve, there is a progressive lipemia up to the five-hour period, when the procedure was terminated. Hence one may well anticipate that in a 24-hour period a large portion of the butter fat was absorbed, since steatorrhea to a degree associated with diarrhea was not noted among patients during therapy. Black and Simpson [18] also have commented on the disparity between oral fat tolerance curves and fecal fat excretion among military patients in India.

At the present time the interpretation of the continued impairment of vitamin A absorption is puzzling. The normal serum levels of the control subjects was similar to values observed in the United States. The dietary intake of the sprue patients and control subjects was identical, so that the poor absorption curves noted in the sprue patients do not reflect inadequate dietary intake of vitamin A. Patients were evaluated to eliminate diseases associated with low vitamin A serum levels. This oral tolerance test may well be the last absorption alteration to show improvement. Suarez [19] has suggested that the gastrointestinal tract may have permanent alterations of function in some treated patients. Although poor absorption is observed in tropical sprue, the possible association of other metabolic disorders to depress serum levels does not make this procedure as helpful as butter-fat absorption in evaluating patient's progress. The prolonged depression of fasting serum

values for vitamin A and carotenoids also indicates persistent malabsorption of vitamin A and precursors.

In many respects the type of tropical sprue with macrocytic anemia observed in Puerto Rico is similar to the descriptions of the syndrome by British workers in India. The patients included in the present study have been classified by the definition of Suarez.[20] The presence of a continued defect in absorption demonstrated by these oral tolerance tests may indicate permanent alterations in the rate of small-bowel absorption. One must therefore conclude that the disease is associated with changes in bowel function which are not affected dramatically by prolonged folic acid or vitamin B_{12} therapy. Recent studies have indicated no alterations in the bacterial flora of the bowel walls.[21] Measurements of mucoproteins in small-bowel juice obtained from the jejunum have indicated decreased concentrations of soluble mucoproteins before and during treatment of tropical-sprue patients.[22] Abnormal cytological changes of the gastric columnar cells are observed in untreated tropical sprue which appear to be identical with epithelial alterations noted in pernicious anemia.[23] Despite prolonged treatment these abnormalities persist even in the presence of free gastric acidity in the treated sprue patient. Possibly similar cellular changes exist in the small bowel in association with the altered mucoprotein secretions. Preliminary studies also have demonstrated poor oral absorption of iron and radioactive labeled vitamin B_{12} after prolonged therapy with folic acid.

These absorption studies do not explain the syndrome of tropical sprue. These observations indicate that the small-bowel malabsorption defect exists before therapy and is not improved markedly by hematopoietic agents. Two interpretations may be made: (1) Prolonged malnutrition has altered gastrointestinal function so that some irreversible absorption defects persist, and (2) a primary absorption alteration exists as the genesis of the sprue syndrome and does not respond completely to nutritional therapy. Correction of anemia is associated with improvement of the diarrhea. This change may be associated with anemia per se as noted in pernicious anemia.[1] However, in some instances despite adequate folic acid and/or vitamin B_{12} therapy, improved blood values, and careful dietary programs, small-bowel absorption defects may cause recurrent diarrhea.

Summary

Oral tolerance tests utilizing D-xylose, butter fat, and vitamin A have been performed in tropical-sprue patients before and during therapy. Poor absorption of these foodstuffs was noted before treatment. Although patients had good hematological responses, only minimal improvement in the tolerance tests was observed with therapy. The persistent malabsorption suggests that the correction of the hematological nutritional defect is not associated with recovery from small-bowel dysfunction. Such studies would indicate that tropical sprue as observed in Puerto Rico is not a reversible nutritional deficiency.

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Chronic Esophagitis

A Possible Factor in the Production of Carcinoma of the Esophagus

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The etiology of cancer is yet unsolved. Similarly, the relative importance of hereditary and environmental factors remains to be proved. There are variations in the incidence of cancer dependent upon racial, sex, hereditary, geographic, environmental, economic, social, and occupational factors. Chronic irritation to the skin and mucous membranes has long been thought to be a possible carcinogenic agent, whether this be traumatic, chemical, thermal, or bacterial. The relationship of chronic esophagitis to the subsequent development of malignancy has never been too well emphasized.

Reports [1] have shown that patients afflicted with carcinoma of the esophagus come generally from a lower economic strata. This is probably a reflection of dietary habits. There seems to be a sex variation in that males for the most part have a higher incidence than females. However, in certain geographic locations, such as Mexico and certain parts of Scotland, females are equally affected. As Steiner [2] points out, there is some racial variation in the incidence of carcinoma of the esophagus; but, except in rare instances, migrant races usually have a similar incidence to the native population. The high incidence of carcinoma of the esophagus in the Chinese and Japanese and low incidence among the Filipinos and Mexicans is difficult to explain on an environmental or dietary basis alone. The thermal factor has been alleged by some * as being a factor in the development of esophageal carcinoma in Scotch females and Russian Jews (hot tea) and in Chinese males (hot rice). Others † have noted a high incidence of chronic alcoholism. In further support of the theory of chronic irritation of the esophagus from alcoholism is the report of Clemmesen [8] (Denmark, 1941), who showed a higher incidence and mortality from carcinoma of the esophagus in hotel and restaurant workers and commercial travelers, and Versluys [9] (Netherlands, 1949), a higher incidence in bartenders, general laborers, fishermen, and commercial travelers. Syphilis has been reported by Tomlinson and Wilson [10] as present in 65% of the British West Indian Negroes so affected, as contrasted to 8.7% of the general necropsy incidence. The fact that most carcinomas of the esophagus occur at the three points of anatomical constriction would be difficult to explain on a racial or geographical basis and points more to a source of chronic irritation at these points of narrowing.

Chronic irritation resulting in esophagitis and esophageal ulceration persisting over a long period of time undoubtedly is a factor little emphasized as a precursor of carcinoma of the esophagus. Such irritation may be classified as extrinsic, i.e., irritating foods or drink taken orally over a period of years with sufficient frequency, or intrinsic, secondary to stasis, infection, or gastric regurgitation. Most physicians caring for patients with esophageal diseases have noted in their experience occasional patients with previous lye burns and strictures who developed carcinoma after a period of years. The authors have had two such instances in a group of 50 patients with lye burns of the esophagus. Vinson,[11] in 1940, reported

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* References 3 and 4.

† References 5-7.

having seen six patients with esophageal carcinoma who previously had lye burns of the esophagus. Benedict [12] has reported 3 such occurrences, and Kiviranta [13] noted 9 in a group of 381 patients having erosive strictures. In his series this was a thousandfold greater than the incidence of carcinoma of the esophagus in the general population of Finland.

The purpose of this paper is to further stress the importance of chronic irritation in the form of esophagitis as a likely cause of malignancy. This report is based upon 10 patients with carcinoma of the esophagus, 7 of whom had an associated hiatal hernia, 2 a pulsion diverticulum of the lower esophagus, and 1 achalasia of the esophagus.

The 7 patients who developed carcinoma of the esophagus associated with hiatal hernia were from a total group of over 200 patients with this latter condition. In a survey by the National Cancer Institute [14] in 1947 and 1948, the incidence of carcinoma of the esophagus per 100,000 population in the seven cities sampled varied with whites from a high in Chicago of 6.7% to a low in Dallas of 2.4%. A similar comparison based on the incidence in this group would be 3500 per 100,000. In other words, a patient with a hiatal hernia has almost a thousandfold chance of developing a carcinoma as compared to the general population. In further support of this theory of chronic irritation from a hiatal hernia or regurgitant esophagitis as a possible precursor of malignancy is the fact that the greater proportion of patients with esophagitis have as their location of involvement the lower esophagus. Similarly, carcinoma of the esophagus is most commonly found in the lower esophagus.

The few previous reports pertaining to the relationship of carcinoma to hiatal hernia have suggested their infrequent association.[15] In a group of 3448 patients having gastrointestinal x-rays, studied by Brick,[16] 705 (20.41%) had duodenal ulcers, 308 (8.93%) hiatal hernia, and 101 (2.92%) carcinoma of the stomach. Of the 308 cases of hiatal hernia, 2 had an associated gastric carcinoma and 1 an esophageal carcinoma. To Brick, this analysis suggested an infrequent relationship. Brick reviewed the literature to 1949 concerning gastric carcinoma associated with hiatal hernia. Of the 23 cases reported in which the location was given, the carcinoma was in the cardia in 13 patients and elsewhere in the stomach in the other 10. Carcinoma of the esophagus was not mentioned. Holland and Logan [17] reported a 74-year-old white man with a hiatal hernia and irregular outline in the lower esophagus who was esophagoscoped by Jackson for dysphagia. A biopsy showed ulcerative esophagitis. This was repeated one year later with a diagnosis of Grade 4 carcinoma. Jackson commented that though he had seen a few cases in whom carcinoma developed in herniated portions of stomach, he did not feel that hiatal hernia was a causative factor. Harrington [18] reported 5 instances of carcinoma of the stomach (location not listed) out of 223 operations for hiatal hernia. Robb,[19] in 1953, and Smith, in 1955,[20] reported four additional instances of malignancy associated with hiatal hernia. Olsen and Harrington [21] reported 3 patients with carcinoma of the cardia in 220 cases of shortened-esophagus type hernia, and an additional similar case was reported by Dawson and Richards.[22]

According to Brick, occurrence of carcinoma of the esophagus and hiatal hernia in the same patient was very uncommon. Moller [23] reported two cases from the literature, Magnes and Clerf [24] saw three cases associated with shortened-esophagus type hiatal hernia. Wolf [25] reported the necropsy findings of a carcinoma of the esophagus associated with a hiatal hernia. Raven [26] reported occurrence of carcinoma of the esophagus in a 58-year-old man in shortened-esophagus hiatal hernia. Harrington [18] operated on three patients with esophageal carcinoma and hiatal hernia, and Olsen and Harrington [21] reported one other case of carcinoma of the esophagus with hiatal hernia. Smithers [27] reported four similar cases of his own and mentioned two others

in 1952. There are undoubtedly others in the literature not noted, as well as others not recognized or reported.

Most of the literature pertinent to this possible relationship has been relatively recent. As its possible significance is recognized, undoubtedly more cases will be reported. One must conclude, however, that those patients with hiatal hernia who develop an esophagitis may have a greater potentiality of developing subsequent malignancy than those without esophagitis or the population in general.

Symptoms from hiatal hernia are largely the result of the associated esophagitis. Such symptoms may in some instances be controlled by medication. In others, surgical therapy is necessary. Usually only the patients with severe or uncontrollable symptoms are surgically treated. Some patients with chronic irritation at this site are self-medicated; some have intermittent medical management, and in some the symptoms are never severe enough to require treatment for many years. Perhaps surgeons have been amiss for not recognizing the potentiality of malignancy at this site in patients with hiatal herniae and stressing the wisdom of correcting this source of danger.

The history and clinical course of all of these seven patients were quite similar and were characterized by gas, indigestion, belching, occasional episodes of dysphagia, and night pain relieved by rising. Three of the patients had been previously treated for ulcers, two took self-medication in the form of "Tums," and the other two ignored their symptoms. The above symptoms had persisted for 7 to 20 years. Only two of the patients had had previous roentgen diagnoses of a hiatal hernia. Five of the patients had sliding hiatal herniae, and two were of the shortened-esophagus type. Because of their previous symptomatology, they all delayed seeing their physician when difficulty in swallowing developed until the malignancy in each case was quite advanced. In five of the patients, adenocarcinomas arising in the cardia of the stomach and extending into the distal esophagus were present, and in the other two squamous-cell carcinomas were found with secondary cardial invasion. Case 1 typifies the patient with a hiatal hernia who subsequently developed a carcinoma.

Case 1.—A man aged 50 was first examined in December, 1952, because of increasing dysphagia of three and one-half months' duration. There had been a recent weight loss of 20 lb. He related that he had had intermittent episodes of indigestion, gas, belching, heartburn, and night pain relieved by getting up and taking soda since the age of 20. The physical examination was essentially negative. Barium roentgen examination of the esophagus revealed the presence of a sliding hiatal hernia with an irregular filling defect and some obstruction in the distal esophagus (Fig. 1). Esophagoscopic examination revealed a malignant

Figure 1

growth in the distal esophagus from which a biopsy was taken. This was reported as an adenocarcinoma. A thoracotomy was performed, with resection of the carcinoma which involved 2 in. (5.1 cm.) of the distal esophagus as well as the cardia of the stomach. The typical findings of a hiatal hernia were also present.

Admittedly the total number of patients seen with a co-existing hiatal hernia and a carcinoma will not be great. Also, the development of malignancy in the distal esophagus or cardia of the stomach with secondary esophageal obstruction in patients

with previous hiatal herniae does not necessarily point to a cause-and-effect relationship. However, the increasing number of such reports and the fact that hiatal herniae may cause chronic esophagitis with ulceration and metaplasia should make physicians cognizant of this possible danger.

We have recently reviewed [28] a series of 55 patients with esophagitis treated between Jan. 1, 1949, and Jan. 1, 1955, of whom 41 (75%) had an associated hiatal hernia. Eighteen of these patients were treated by repair of the hiatal hernia with complete amelioration of symptoms. In those cases treated medically with antiacids and dilatation, the majority with a severe esophagitis continued to have significant symptoms in spite of treatment. Hence, in our experience it has been possible to control the associated esophagitis with its possible carcinogenic potential by hiatal hernia repair.

Esophageal Diverticulum with Carcinoma

In a previous report [29] by one of us the relationship of achalasia of the esophagus and pulsion diverticulum of the lower esophagus was discussed. It is our opinion that achalasia of the esophagus results from a parasympathetic imbalance probably resulting from trophic changes in Auerbach's plexus, causing failure of relaxation and hypertrophy of the inferior esophageal constrictor. Initially there is increased esophageal peristalsis, and, in turn, increased intraluminal pressure to overcome this neuromuscular esophageal occlusion. Anatomically, it has been demonstrated that the inner circular layer of muscle fibers is incomplete in the lower esophagus, so that weak areas result in which the mucous membrane is unsupported by inner muscular layers. Functional obstruction at the level of the inferior esophageal constrictor and increased intraesophageal pressure would predispose to diverticula.

The esophagitis present both within the diverticulum and about its orifice coupled with the delayed emptying action of the esophagus would further aggravate this condition. Reports are even less meager in reference to the development of carcinoma in patients with esophageal diverticula. Crile and Dinsmore [30] reported in 1924 a case of a man aged 55 who had multiple esophageal lesions, including cardiospasm, a diverticulum, and a carcinoma. In 1927, Vinson [42] reported three such cases, one of which arose within the sac of the diverticulum. The majority of recorded instances of carcinoma developing in esophageal diverticulum have been of the pharyngoesophageal variety. There have been 12 such instances noted by Riberi, Battersby, and Vellios [32] in 1955. In a review of the literature they emphasized the greater incidence of carcinoma in patients having diverticula than in the general population and attribute the development of carcinoma to the associated chronic inflammation and ulceration.

In our series of 12 patients with pulsion diverticula of the lower esophagus, 2 (both males) had squamous-cell carcinomas arising at the level of the orifice of the diverticulum into the esophagus. Pulsion diverticula of the lower esophagus usually do not cause significant symptoms until they attain considerable size, at which time dysphagia and pain frequently referred to the back are noted. The history and clinical course of both patients were essentially the same and are typified by the abstract of Case 2.

Case 2.—This 62-year-old man was first seen in January, 1950. He gave a three-year history of substernal and back pain and intermittent difficulty in swallowing. This difficulty in swallowing was progressive for the prior year, so that at the time of the examination he could only swallow semisoft foods. There had been two episodes of hemetemesis within six months. He had lost 40 lb. in weight. The physical examination was essentially negative except for emaciation. Barium roentgen examination of the esophagus showed a large pulsion diverticulum and an irregular filling defect in the esophageal lumen at the same level (Fig. 2). An esophagoscopic examination revealed an irregular mass at the site of the orifice of the diverticulum. A biopsy revealed a squamous-cell carcinoma. A thoracotomy was subsequently performed, with resection of the carcinoma and diverticulum with an esophagogastric anastomosis.

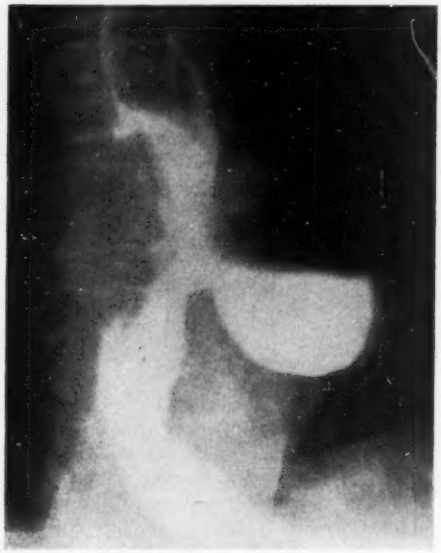

Figure 2

Achalasia of the Esophagus with Carcinoma

Reports ‡ of the existence of a carcinoma in patients with achalasia have been more frequent but have consisted mainly of isolated case studies. One would expect the incidence of carcinoma developing in patients with achalasia to be considerably greater in view of the long duration of stasis, esophagitis, and ulceration existing in such patients. However, reports show diverse opinions as to its frequency. Gottstein [36] was one of the first to suggest this relationship, in 1908, when he reported 33 patients with achalasia, 3 of whom had coexistent malignancy. In 1931, Rake [37] reported 3 cases in a series of 15 patients with achalasia. However, on the other hand, other reports suggest their infrequent occurrence. Olsen and his associates,[38] in 1951, reported 1800 cases of cardiospasm and do not mention malignancy as a complication. A total of 18 cases had been collected from the literature by Baer and Sicher [39] by 1947, at which time they reported an additional one of their own. Other isolated instances have been reported since, but most such reports § do not relate how large a group of patients their total experience included. The 1 patient with achalasia noted in our experience who developed a carcinoma was from a group of 75 such cases. The detection of a carcinoma in patients with achalasia is particularly difficult in view of the fact that dysphagia has usually existed for some time and does not increase with the development of malignancy. One of the most characteristic signs is the presence of anemia and hemetemesis, which was present in our case as well as noted in many instances of those reported in the literature. Unfortunately, this is a late sign resulting from ulceration of the carcinoma. Another sign that was apparent to the patient and obvious to the examiner was a very foul odor to the breath caused by necrosis of the malignancy. The clinical abstract of this patient is presented in Case 3.

Case 3.—This 51-year-old man had had symptoms of achalasia for 12-20 years. One year prior to being seen he had been operated upon elsewhere for relief of the achalasia through an abdominal approach, with some benefit. An esophagoscopy had not been performed. During the year prior to our examination, in November, 1955, he had had several tarry stools and hemetemesis and had become progressively anemic. The esophagus had been examined roentgenologically upon two occasions with barium, but in each instance the food content of the esophagus had not been evacuated. There had been a recent loss of weight of 20 lb. An esophagoscopic examination was performed which showed an extensive squamous-cell carcinoma of the midesophagus. This was followed by a barium roentgen examination of the esophagus while the esophagus was empty of its food content, and a large carcinoma was easily visualized (Fig. 3). A thoracotomy was performed, but the carcinoma was found to be inoperable.

Again the exact relationship of achalasia and the development of carcinoma of the esophagus cannot be stated. However, the increasing number of reports describing their coexistence should make physicians aware of this possible danger. Patients with achalasia should have roentgen examinations of their esophagus only after evacuation. A roentgenologist insists on enemas prior to examination of the colon but rarely insists

‡ References 33-35.

§ References 40-42.

Figure 3

that the esophagus be cleansed prior to examination of this organ. Also, one should not be content with a roentgen examination alone but should insist on an esophagoscopic examination, where the entire esophageal mucous membrane can be visually inspected.

Comment

Chronic irritation is generally considered to be a factor in the production of malignancy. This irritation in the esophagus may be the result of chronic ulceration secondary to lye burns, peptic esophagitis associated with hiatal herniae, or bacterial as a result of stasis and infection in patients with achalasia of the esophagus and diverticulum. Though many patients with each of these conditions do not develop malignancy, it is probably unwise to allow any of these conditions to persist untreated when complicated by a significant esophagitis. The recognition of this complication must be acknowledged, the proper examinations frequently made, and the indicated therapy provided to eliminate chronic esophagitis when present, to avoid the possibility of later malignancy supervening. No examination is complete without examining the esophagus by x-ray only after proper cleansing and by the esophagoscope, where the mucous membrane may be directly visualized. Ten patients have been reported with chronic esophagitis who have subsequently developed carcinoma. Seven of these patients have had hiatal herniae, two were associated with esophageal diverticulum, and one patient had achalasia.

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Unilateral Clubbing Following Traumatic Obstruction of the Axillary Vein

Report of a Case

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The pathogenesis of symmetrical digital clubbing has been widely discussed, but no definitive conclusions have ever been reached. Among the chief difficulties present in attempted solutions of this problem has been the extremely large variety of apparently unrelated clinical conditions in which clubbing has been found.[1] Of special interest, therefore, as offering possible clues to basic pathogenesis are the occasionally reported cases of unilateral, asymmetrical, or unidigital clubbing.

Reported cases of unilateral clubbing prior to 1943 have been summarized by Sartor.[2] This and other reports * yield the following information: There were 33 recorded cases of unilateral clubbing in which an aneurysm was present in relationship to the major vessels of the involved extremity. In two cases of this group, there was in each an aneurysm proximal to a coarctation of the aorta. There were three cases associated with arteriovenous aneurysm and two with nonaneurysmal dilatation of an artery. Five were found related to carcinoma of an upper-lobe bronchus or superior sulcus tumor. Single case reports were associated with the following conditions: phlebectasia of an upper extremity,† scapulohumoral subluxation, median nerve injury, and absent aortic arch. In this last case [8] the blood supply reached the left arm and lower extremity via the pulmonary circulation and there was clubbing of the digits of the left hand and of both feet.

Wilson's two reported instances of asymmetrical regression of clubbing are of interest.[7] The first was that of a 61-year-old man with bilateral clubbing secondary to chronic pulmonary infections. During surgical drainage of a tuberculous abscess of the left axilla, the axillary artery was ligated. Subsequently clubbing of the fingers of the left hand regressed. The second, that of a 13-year-old boy with the tetralogy of Fallot, showed regression of left-hand clubbing following the anastamosis of the left subclavian and pulmonary arteries. The report by Lukas and co-workers [9] is also of interest. They studied reversal of flow in patent ductus arteriosus in four patients. In two of these they noted clubbing of the toes but the absence of clubbing in the fingers.

A case of unilateral clubbing in a patient with traumatic obstruction of the subclavian vein was studied recently. This combination appears to be unique, since no report of such an association has been found in the literature; it is considered worthy of report.

Report of Case

The patient was a 28-year-old white man admitted to the East Orange Veterans Administration Hospital on July 26, 1954, with complaints of hemoptysis and pain in his right arm. His present illness began in 1945, when he sustained a gunshot wound in combat. The missile entered the middle of the right clavicle and came out in the right lower posterior axillary region. A thoracotomy was done at a field hospital, and lacerations of the lung and diaphragm were repaired. His post-

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From the Medical Service, Veterans Administration Hospital.

* References 3-8.

† Although the case reported by Souques [6] has been listed as "phlebectasia" by Mendlowitz,[1] it was probably complicated by subclavian aneurysm. The Wasserman reaction was positive. The only acceptable case of primary pathology of the veins resulting in clubbing was that of Mendlowitz.[5]

operative recovery was uneventful except for a temporary hemothorax. A dry cough, present immediately after the operation, became productive in about three months of blood-streaked sputum. Since then, intermittent hemoptysis has continued, varying from mild blood streaking to expectoration of 5 oz. of grossly bloody material. He was hospitalized on three occasions for the above symptoms and had twice undergone bronchoscopy and bronchography.

In 1950 the patient noted the insidious onset of a numbness and pain which would start in his right clavicular area and radiate down the posterior aspect of his arm and medial aspect of his forearm to his wrist. The discomfort was aggravated by activity and relieved by rest. About one year after the onset of the pain he noticed clubbing of the fingers of his right hand. This clubbing progressed slowly.

Physical examination revealed a well-developed man not appearing ill. Blood pressure in the right arm was 130/90 mm. of Hg and in the left arm, 130/80 mm. of Hg. The chest showed a 3 cm. scar over the midright clavicle, and there was an accentuation of the anterior bowing of the right clavicle. An 8 cm. thoracotomy scar running parallel with the posterior axillary line was present over the lower right posterior hemithorax, and the defect resulting from the surgical removal of portions of the 9th and 10th posterior ribs was palpable. At this site paradoxical movement of the chest wall was evident. Except for moderate diminution of transmission of breath sounds in the region of the operative scar, no abnormalities were present on auscultation of the lungs. A Grade 1 systolic murmur, believed to be functional, was audible over the apex of the heart. The right arm and forearm were grossly larger than the left.‡ There was distinct clubbing of the distal phalanges of the right hand (Fig. 1), and a faint cyanosis of the nail beds of the right hand was visible. A dilated collateral venous circulation around the right shoulder girdle was noted (Fig. 2).

Fig. 1.—Photograph of hands, illustrating clubbing and hypertrophy of right hand.

Laboratory data included normal blood cell counts and urinalyses and a negative VDRL. Sputum cultures yielded no pathogens. The posterior anterior chest x-ray revealed a localized clouding in the right second anterior intercostal space overlying the second and third anterior ribs and a small comma-shaped opacity overlying the lower border of the right fourth anterior rib. The thoracotomy rib defect and obliteration of the right costophrenic angle were also noted. On lateral views the clouding in the right second anterior intercostal space was localized posteriorly and was thought to represent pleural reaction following passage of a foreign body. It was felt that the comma-shaped opacity represented retained iodized oil (Lipiodol), since it appeared to change in shape on serial films. A bronchogram (Fig. 3) showed a localized saccular bronchiectasis, thought to lie in the posterior segment of the right lower lobe. X-ray of the right shoulder showed a healed fracture deformity of the middle third of the clavicle, with slight upward bowing. X-rays of the hands showed increase in soft-tissue fullness of the distal phalanges of the right hand

‡ Measurements of the circumferences of both arms at various levels were as follows: Deltoid insertion, right 32.7 cm., left 30.0 cm.; midarm, right 32.5 cm., left 28.4 cm.; elbow, right 30.5 cm., left 28.4 cm.; 6 cm. below the elbows, right 31.0 cm., left 29.2 cm.; wrist, right 19.0 cm., left 17.8 cm. The widest distal phalangeal diameters were as follows: Right, (1) 2.5 cm., (2) 2.2 cm., (3) 2.1 cm., (4) 2.1 cm., (5) 1.9 cm.; left, (1) 2.0 cm., (2) 1.9 cm., (3) 2.0 cm., (4) 1.8 cm., (5) 1.6 cm.

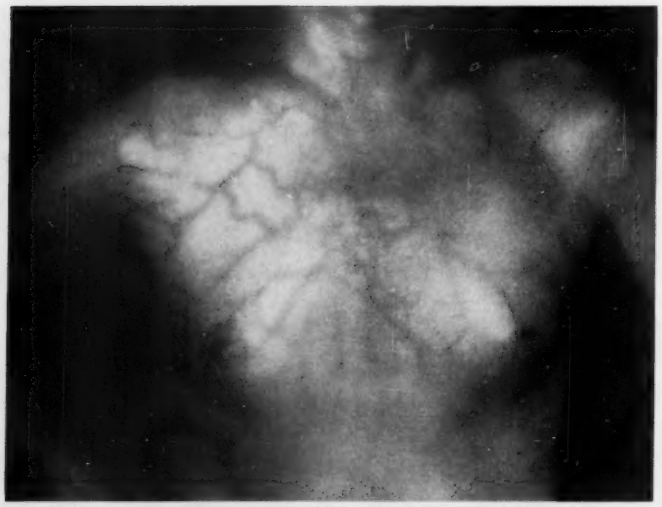

Fig. 2.—Infrared photograph of chest and shoulders, illustrating dilated collateral venous circulation about right shoulder girdle.

Fig. 3.—Bronchogram, showing localized saccular bronchiectasis.

in comparison with the left hand. There were no bone or joint changes. A venogram and part of the angiocardiogram (Fig. 4) indicated obstruction of the first portion of the axillary vein, dilatation of the axillary and brachial veins, and an extensive collateral circulation originating in the region of the venous obstruction. An angiocardiogram did not confirm a suspicion of pulmonary arteriovenous fistula.

Spirometric studies were within normal limits. An arterial oxygen saturation was 94.8 %, and arterial carbon dioxide content, 51.3 vol. %. The electrocardiogram was within normal limits.

Venous pressure in the right antecubital vein was 220 mm. of Hg, and in the left, 94 mm. Arm-to-tongue circulation time measured with dehydrocholic acid (Decholin) was 11.0 seconds, and arm-to-lung circulation time measured with ether was 7.0 seconds. A bronchoscopic examination was normal.

After study, the established diagnoses arrived at were obstruction of the venous drainage of the right upper extremity and a small localized bronchiectasis in the posterior basal segment of the right lower lobe.

Resection of the posterior and lateral basal segments of the right lower lobe was performed on Oct. 1, 1954, in an attempt to control hemoptysis. Evidence of chronic inflammatory change was noted in the pathologic studies of the resected specimen.

Follow-up on several occasions until September, 1955, has revealed no significant change in the patient's symptoms. His hemoptysis persisted.

Comment

The terms clubbing and hypertrophic pulmonary osteoarthropathy are often used interchangeably. A distinction has been drawn between these terms, however.[10] The former represents a "uniform painless en-

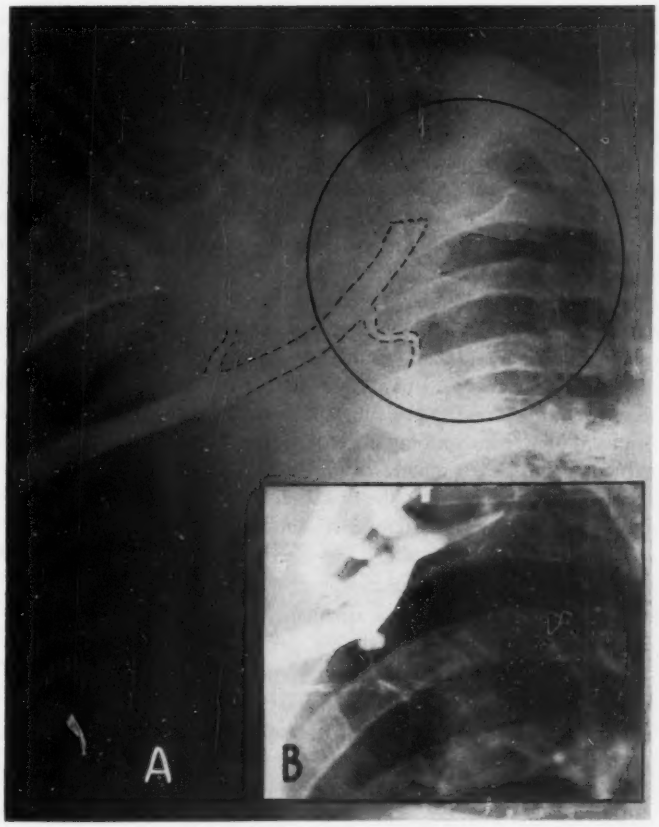

Fig. 4.—*A*, venogram, illustrating dilation of axillary vein and filling of collaterals. The vein is outlined. *B*, section from the angiocardiogram, showing obstruction of the axillary vein more sharply because of higher concentration of dye obtained during procedure.

largement of the tips of the fingers and toes," and the latter, a severer degree of this process involving more proximal parts, and at times causing pain.

Despite the numerous reports concerning clinical aspects and pathogenesis of clubbing, descriptions of the pathological changes in the clubbed digit are sparse. Gall and co-workers,[11] in a study of tissues obtained from seven cases, described the histological changes in the clubbed digits; this consisted of a proliferation of the periosteal layers and new bone formation, edema, collagen swelling, and inflammatory infiltration of soft tissues adjacent to the periosteum. Vascular changes consisted of thickening of the walls of the small- and medium-sized blood vessels adjacent to the periosteum. Lovell[12] stressed another aspect of the pathology of clubbing in differentiating the changes that occur in congenital heart disease from those in bronchopleural disease. In the former he demonstrated that the size of the clubbed digit could be reduced more than the normal digit by exsanguination. In the latter he was unable to effect significant reduction in the size of the clubbed digit through this procedure. He concluded that an increase in connective tissue was a major component of clubbing in all diseases, but that in addition congenital heart disease presented the feature of increased blood volume in the venous plexuses. This was demonstrated by autopsy studies employing a specially developed technique of vascular injection.

Because of the many apparently unrelated conditions associated with clubbing, a multiplicity of theories attempting to explain the pathogenesis of clubbing has arisen. As ex-

amples, the following may be mentioned: toxemia,[13] anoxia and passive congestion,§ impaired tissue nutrition on the basis either of low oxygen tension or of clumping of red blood cells,[16] endocrine imbalance,[17] combined neurological and endocrine factors,[18] and multiple causes.[2] The historic development of these theories has been discussed by Mendlowitz.[1] Each theory in most instances appears to be capable of explaining the appearance of clubbing under a limited set of circumstances. The studies dealing with the dynamic aspects of the circulatory changes in the involved digits and extremities have, in contrast to previous approaches, been productive in bringing about a uniform explanation of all instances of clubbing.

Since clubbing involves the distal phalanx almost exclusively, it is natural to look for structural peculiarities which may explain this localization. The glomus appears most capable of fulfilling this requirement. The distribution of the glomus closely parallels the distribution of clubbing. The glomus is a highly specialized arteriovenous anastomosis anatomically well adapted to its role as a regulator of digital circulation.[19] It consists of an afferent artery joining the so-called Sucquet-Hoyer canal. The canal is made up of a complex arrangement of smooth muscle and epithelioid cells surrounded by a richly innervated collagenous reticulum. An elastic lamina produces a valve-like ruffle at the entrance to the canal, and from this point two to five arterioles arise which subdivide into capillaries supplying the canal and related structures. The venous portion consists of a voluminous receptacle forming a cape around the glomus and emptying into the subpapillary and deep veins of the digit.[20] The distribution of these structures has been described by Grant and Bland[19] and Popoff.[20] Although their figures differed in absolute numbers, since different counting techniques were employed, they were in agreement on the relative numbers of glomera in different areas.‖ The influence of age on the number of glomera is of interest in light of the observation that clubbing is greater in comparative youth.[14] Popoff[20] stated that the Sucquet-Hoyer canals disappear after the age of 60. The function of the glomus is intimately concerned with temperature regulation[19] and is responsible for the normally increased blood flow to the distal phalanx observed by Wilkins and co-workers.[21]

While no direct evidence, either physiological or pathological, proving the role of the glomus in the genesis of clubbing is available, various methods have been employed to demonstrate the increase in blood flow in clubbed fingers. Since the glomus is the chief regulator of blood flow in the distal phalanx, its role is therefore inferred to be of major importance.

Charr and Swenson[22] demonstrated increased vascularity of clubbed fingers by infrared photographs and by postmortum injection of a thin barium suspension into the circulation. Mendlowitz[23] studied digital blood flow and brachial-digital blood pressure gradients in normal subjects and in patients with essential hypertension, aplastic anemia, hyperthyroidism, acromegaly, and various infections. He was unable to demonstrate any pattern of increase in blood flow per unit of surface or volume of fingertip in any of these conditions. Excessive blood flow and a decreased brachial-digital blood pressure gradient was demonstrated, however, in simple clubbing. An increase in blood flow, decrease in brachial-digital blood pressure gradient, and a decrease in arterial-venous oxygen difference were demonstrated in an extremity showing clubbing in association with a right axillary syphilitic aneurysm when compared with the contralateral arm, which had a normal circulation.[3] A crude model of the

§ References 14 and 15.

‖ The figures of Grant and Bland,[19] obtained from a 35-year-old man, indicated that the numbers of glomera per square centimeter were as follows: nail bed, second toe, 593; pad, second toe, 293; sole, near heel, 197. No glomera were present in the skin of the dorsum of the foot, lower calf, or lower half of an ear.

subject's arterial circulation was then constructed, and it was shown that the flow on the side containing a distensible sac was increased only if a valvular mechanism was present at the proximal entry so that added fluid from the elastic recoil of the sac was directed distally. This study appears to be a significant contribution in explanation of the mechanism of unilateral clubbing associated with aneurysm.

From the studies previously mentioned it seems that an increase in acral blood flow is a prerequisite for the development of clubbing. This was further qualified by Lovell,[12] who stated that fibrosis results from blood flow in excess of tissue requirements and believed that the changes were due to a "forced feeding." He attributed the localization of the connective tissue proliferation between the nail and phalanx to the observed preponderant distribution of glomera in this region. Further support is lent to this hypothesis by the work of Mendlowitz,[24] the only investigator successful in producing clubbing experimentally. He demonstrated that when increased cardiac output resulted from anastomosis of the pulmonary artery to the left atrium of a dog, clubbing appeared. Wilson[7] observed unilateral clubbing in two cases of arteriovenous aneurysm of the extremity in which peripheral blood flow was increased on the side of the lesion. He noted that this was an uncommon finding in arteriovenous aneurysm and occurred only under the circumstances of increased blood flow distal to the lesion.

Clubbing and hypertrophic pulmonary osteoarthropathy appear to be caused by an increase in blood flow beyond the tissue requirements. This increase in flow may result from multiple causes. Thus, each of the proposed theories of the pathogenesis of clubbing and hypertrophic pulmonary osteoarthropathy is probably correct in its limited sphere. In the light of the studies presented, one may speculate that neurogenic, toxic, anoxic, endocrine, and other factors known to be associated with clubbing result in the "forced feeding" of acral tissues described by Lovell[12] through mechanisms not fully understood as yet. The extreme rarity of clubbing resulting from venous occlusion is probably related to the observation that venous occlusion causes a decrease in arterial flow.[25] A possible explanation of the mechanism in the case presented might be dilatation of the arteries and arterioles resulting from long-standing marked venous obstruction in the involved extremity. The blood flow might then increase as a result of the overcompensated lowering of the peripheral resistance and increased vascular bed, as suggested by Mendlowitz.[5] The contribution, if any, of the localized lung lesion cannot be assessed. Because of the unilateral localization of the clubbing, it may be assumed to be unrelated.

Summary

A brief analytic survey of the literature on unilateral clubbing is presented. It is noted that the most frequent associated condition is an arterial aneurysm in relationship to the involved extremity. The case of a 28-year-old man with a history of a gunshot wound of the chest with resulting injury of the right axillary vein and pulmonary parenchyma is presented. The patient entered the hospital primarily because of hemoptysis, which was attributed to a localized bronchiectasis. Coincidentally it was noted that the fingers of the right hand were clubbed and the entire extremity was hypertrophied. An obstruction of the first portion of the right axillary vein with development of extensive collaterals and an elevated venous pressure were demonstrated. The pathogenesis of clubbing is briefly reviewed. An increase in peripheral blood flow beyond the tissue requirements is considered to be the major prerequisite for the development of clubbing. The probable role of the glomus is also considered.

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Fatal Acute Myocardial Infarction in Diabetic Patients

A Comparative Study of Ninety-Four Autopsied Diabetics with Acute Myocardial Infarction and Four Hundred Six Autopsied Nondiabetics with Acute Myocardial Infarction, with Special Reference to Age and Sex Distribution

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It has been clearly demonstrated in numerous clinical and anatomical studies that arteriosclerosis and its complications are commoner in patients with diabetes mellitus than in nondiabetic patients.* In the autopsy series at Washington University, diabetes mellitus is three times as common among men with acute myocardial infarction as among men in the general autopsy population. The corresponding ratio for women in this series is 4:1.[7]

Thus, the close association between diabetes mellitus and acute myocardial infarction is well known. However, inadequate information is available regarding the clinical and anatomical features of diabetics with acute myocardial infarction as compared with the corresponding characteristics of nondiabetics with acute myocardial infarction. The purpose of this report is to present the clinical and anatomical features in 94 diabetics who died with acute myocardial infarction compared with those in 406 nondiabetics who died with acute myocardial infarction.

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Material and Methods

During the period 1910-1954, a total of 500 autopsies were performed in the Department of Pathology of Washington University on patients from Barnes Hospital with anatomical evidence of acute myocardial infarction. Among these 500 there were 94 (42 men, 52 women) who also had diabetes mellitus. These will be referred to hereinafter as the "diabetic-myocardial infarction group." The remaining 406 (293 men, 113 women) had no clinical or anatomical evidence of diabetes mellitus and will be referred to as the "nondiabetic-myocardial infarction group." The clinical and autopsy records of these patients were reviewed, and pertinent clinical and anatomical features were tabulated separately for the diabetics and nondiabetics.

Results

The results of the study of the 500 patients with acute myocardial infarction are summarized in Tables 1-4. The average age of the patients in the diabetic-myocardial infarction group was 63 (men 61; women 64) as was the corresponding age for the nondiabetic-myocardial infarction group (men 62; women 64). The distributions of the ages in the two groups (diabetic-myocardial infarction and nondiabetic-myocardial infarction) were also similar, as shown in Table 2. Seventeen of the men in the diabetic-myocardial infarction group were known to have had diabetes for more than five years. Their average age was 58. The corresponding average age for 24 women who were known to

TABLE 1.—*Clinical and Anatomical Features of 94 Diabetics with Acute Myocardial Infarction Compared with the Corresponding Features of 406 Nondiabetics with Acute Myocardial Infarction**

	Diabetic Group			Nondiabetic Group		
	Men	Women	Total	Men	Women	Total
No. of patients	42	52	94	293	113	406
Average age, yr.	61	64	63	62	64	63
More than 10% overweight, per cent†	35	46	41	28	39	31
Hist. of hypertension, per cent	77	67	71	50	74	57
Hist. of congestive failure, per cent	53	58	55	41	55	45
Hist. of angina pectoris, per cent	51	40	45	52	43	50
B.P. < 90 systolic per cent	16	21	19	19	15	18
N.P.N. > 80 mg./100cc., per cent	19	22	21	18	7	14
Hb. < 9 gm., per cent	15	8	13	5	11	7
WBC > 20,000, per cent	18	14	16	21	21	21
Ward patient, per cent	25	51	40	31	39	33
Private patient, per cent	75	49	60	69	61	67
Chest pain, per cent	63	52	57	65	60	64
Marked dyspnea, per cent	35	33	34	35	37	35
Size of infarct, large, per cent	26	30	28	22	19	21
Size of infarct, medium, per cent	58	51	54	56	59	57
Size of infarct, small, per cent	16	19	18	22	22	22
Healed infarct, per cent	53	47	50	48	45	47
Location, anterior, per cent	23	38	31	42	36	40
Location, post., per cent	37	38	38	30	25	28
Location, septum, per cent	12	11	12	8	15	10
Location, other, per cent	28	13	19	20	24	22
Thromboembolism, per cent	33	40	36	37	46	40
Mural thrombi, per cent	51	43	47	44	48	45
Rupture, per cent	5	2	3	6	4	5
Bronchopneumonia, per cent	23	23	23	21	27	23
Effusion pleural or abd. cavity, per cent	23	53	40	29	32	30
Average weight of heart, gm.	535	455	490	550	470	530
Average weight of kidneys, gm.	370	310	335	365	290	335
Average weight of lungs, gm.	1,170	960	1,050	1,360	1,010	1,260

* The percentage listed (except in 3 instances) is that of autopsied patients of the sex and group indicated with the characteristic designated. The exceptions are "N.P.N.," "Hgb.," and "WBC." In these instances the percentage indicated is based only on patients on whom the designated procedure was performed.
† According to the tables for ideal weights of the Metropolitan Life Insurance Company.

have had diabetes for at least five years was 63. Twelve men and seventeen women had had recognized diabetes for more than 10 years. Their average ages were, respectively, 56 and 60. None of these average ages (for 5-year and 10-year duration groups) differs significantly from the average ages of the nondiabetic men and women. Only seven men and three women were known to have had diabetes before the age of 40, and none of these had had diabetes since childhood. Their average ages were, respectively, 48 and 57. The average age of these seven men is significantly less than that of the men in the nondiabetic-myocardial infarction group ($P=0.01$).

Forty-two of the patients in the diabetic-myocardial infarction group were men, and fifty-two were women. The

TABLE 2.—*Age Distribution of Two Groups with Acute Myocardial Infarction*

Age, Yr.	Diabetics						Nondiabetics					
	Men		Women		Total		Men		Women		Total	
	No. of Pts.	Per Cent	No. of Pts.	Per Cent	No. of Pts.	Per Cent	No. of Pts.	Per Cent	No. of Pts.	Per Cent	No. of Pts.	Per Cent
Younger than 45	5	12	1	2	6	6	26	9	11	10	37	9
46–60	9	21	16	31	25	27	111	38	27	23	138	33
Older than 61	28	67	35	67	63	67	156	53	75	67	231	58
Total	42	100	52	100	94	100	293	100	113	100	406	100

TABLE 3.—*Incidence of Acute Myocardial Infarction Among the 379 Diabetics in the Barnes Hospital Autopsy Population in Two Periods*

	Men, per Cent	Women, per Cent	Ratio, Men: Women
1910–1939 136 (73 M., 63 W.) autopsied diabetics	15*	9.5	1.6:1
1940–1954 243 (119 M., 124 W.) autopsied diabetics	26	37	0.7:1
Totals (1910–1954) 379 (192 M., 187 W.)	22	28	0.8:1

* The figures listed are the percentage of autopsied diabetics with acute myocardial infarction among the entire autopsied diabetics for the sex and period designated.

TABLE 4.—*Incidence of Acute Myocardial Infarction Among Nondiabetics*

	Men, per Cent	Women, per Cent	Ratio, Men: Women
1910–1939 3,232 (2,018 M., 1,214 W.) autopsied nondiabetics	2.6*	1.2	2.3:1
1940–1954 4,572 (2,890 M., 1,682 W.)	8.3	6	1.4:1
Total 1910–1954 7,804 (4,908 M., 2,696 W.)	6	3.9	1.5:1

* The figures listed are the percentage of autopsied nondiabetics with acute myocardial infarction among the entire autopsied nondiabetics for the sex and period designated.

corresponding figures for the nondiabetic-myocardial infarction group are 293 men and 113 women. In order to interpret these figures it is necessary to relate them to the distribution of adult (over 20 years of age) men and women with and without diabetes in the entire autopsy population (Table 3). One hundred ninety-two men in our autopsy population (1910-1954) were known to have diabetes mellitus. The incidence of acute myocardial infarction among these 192 men was 22% during the entire period 1910-1954. During the first portion of this period (1910-1939) the incidence among diabetic men was 15%, and during the period 1940-1954 it was 26% (difference not significant, $P=0.1$). The incidence of acute myocardial infarction among the 187 autopsied women with diabetes in the Barnes Hospital autopsy series (1910-1954) was 28%. For the period 1910-1939 the incidence among diabetic women was 9.5%, and for the period 1940-1954 it was 37% (difference significant, $P=0.01$).

The corresponding incidences of acute myocardial infarction among the 4908 nondiabetic men and among the 2896 nondiabetic women in our autopsy series for the period 1910-1954 were 6% for men and 3.9% for women. During the period 1910-1939 the incidence of acute myocardial infarction in nondiabetic men was 2.6%, and during the period 1940-1954 the incidence was 8.3% (difference significant $P=0.01$). The corresponding incidences for women in the two periods (1910-1939 and 1940-1954) were, respectively, 1.2% and 6% (difference signifi-

cant $P=0.01$). The ratio of the incidences of acute myocardial infarction in the two sexes for the various periods can be expressed as follows (male: female in each instance): In the period 1910 to 1939 the sex ratio among diabetics was 1.6:1 (difference not significant, $P=0.5$); and among nondiabetics 2.3:1 (difference significant, $P=0.01$); in the period 1940-1954 the sex ratio among diabetics was 0.7:1 (difference significant, $P=0.05$); and among nondiabetics 1.4:1 (difference significant, $P=0.01$).

Forty-one per cent of the patients in the diabetic-myocardial infarction group and thirty-one per cent of those in the nondiabetic-myocardial infarction group were more than 10% overweight (according to recent tables of the Metropolitan Life Insurance Co.).† The difference between these figures is not significant ($P=0.2$).

Comparative figures for some clinical characteristics in the diabetic-myocardial infarction and nondiabetic-myocardial infarction groups are as follows: "history of hypertension" in 71% of the diabetics and 57% of the nondiabetics (difference significant $P=0.01$); "history of congestive failure" in 55% of the diabetics and 45% of the nondiabetics (difference significant, $P=0.05$); "history of angina pectoris" in 45% of diabetics and 50% of the nondiabetics (difference not significant, $P=0.2$); the nonprotein nitrogen level was more than 80 mg/100 cc. in 21% of the diabetics on whom the test was performed and 14% of the nondiabetics on whom the test was performed (difference not significant, $P=0.1$).

Comparative figures for some anatomical characteristics are as follows: the average weight of the heart was 490 gm. in the diabetic-myocardial infarction group and 530 gm. in the nondiabetic-myocardial infarction group; the average weight of the kidneys in each of the two groups was 335 gm.; 59% of the patients in the diabetic-myocardial infarction group and 47% in the nondiabetic-myocardial infarction group had old myocardial infarcts in addition to acute infarction; endocardial mural thrombi and embolic phenomena were similarly common in the diabetic-myocardial infarction group and in the nondiabetic-myocardial infarction group; 23% of the patients in each group had bronchopneumonia.

Comment

Over-All Incidence.—The incidence of acute myocardial infarction among the diabetic patients in our autopsy series was considerably higher than the incidence of acute myocardial infarction in the nondiabetic autopsy population. The incidence of acute myocardial infarction has increased markedly over the years in the Barnes Hospital autopsy series among both diabetics and nondiabetics.

Age at Death.—The presence of diabetes mellitus did not affect the average age at death from acute myocardial infarction in this series. Even when we established a special group consisting only of patients with acute myocardial infarction who were known to have had diabetes for more than 10 years, their average age was not significantly different from the average age of nondiabetics with acute myocardial infarction.

None of the patients with acute myocardial infarction in this series were known to have had diabetes since childhood. It has been stated that juvenile diabetics often die at an early age of arteriosclerosis.‡ This statement may well be true, but the absence of such patients in our large series suggests that juvenile diabetes accounts for only a small number of patients dying with acute myocardial infarction.

Diabetes mellitus was known to have been present before the age of 40 in only 10 patients in this series with acute myocardial infarction. The average age at death

† References 8 and 9.

‡ References 1 and 10.

in these 10 was significantly less than that of the nondiabetics with acute myocardial infarction. This difference in ages supports the idea that the early onset of diabetes in adults leads to death from arteriosclerosis at an earlier age than otherwise would be expected. The small number of patients involved suggests that this is not an important aspect of acute myocardial infarction.

Sex.—In previous studies § of the Barnes Hospital autopsy series, we demonstrated that a change had occurred in the ratio of the over-all incidence of acute myocardial infarction in the two sexes. In the period 1910-1939 the incidence of acute myocardial infarction in men was twice that in women (ratio 2:1, difference significant) and in the period 1940-1954 the corresponding ratio was 1.1:1 (difference not significant). We also found in the previous studies that the incidence of diabetes mellitus among patients with acute myocardial infarction was similarly common in the two periods (1910-1939 and 1940-1954) in each sex. Hence, we concluded that the changing sex ratio in the two periods could not be accounted for by a change in the incidence of diabetes mellitus.

In the current study the ratio of the incidence of acute myocardial infarction in the two sexes in the Barnes Hospital autopsy series (for the periods 1910-1939 and 1940-1954) was explored further, and some interesting facts became apparent. Among diabetics prior to 1940 there was no significant difference in the incidence of acute myocardial infarction in the two sexes. After 1940 the incidence of acute myocardial infarction among diabetics was significantly greater in women than in men. Among nondiabetics the incidence of acute myocardial infarction was significantly greater in men than in women in both periods (the ratio of men to women was 2.3:1 for the period 1910-1939 and 1.4:1 for the period 1940-1954).

Thus it appears from this study that today a nondiabetic man's chance of dying from acute myocardial infarction is still greater than that of a nondiabetic woman. Whereas among diabetics today the chances of a woman dying from acute myocardial infarction are greater than those of a man.

Other Features.—Most of the other clinical and anatomical features studied in the patients with acute myocardial infarction and diabetes mellitus are similar to the corresponding features in the patients with acute myocardial infarction without diabetes mellitus.

§ References 7 and 11.

Summary

The age and sex distribution and various clinical and anatomical features of 94 diabetics who died with acute myocardial infarction (diabetic-myocardial infarction group) are compared with the corresponding features of 406 nondiabetics who died with acute myocardial infarction (nondiabetic-myocardial infarction group).

The average ages at death are similar in the diabetic-myocardial infarction group in both sexes to the corresponding ages in the nondiabetic-myocardial infarction group.

In previous studies we have demonstrated that prior to 1940 acute myocardial infarction in the Barnes Hospital autopsy series was significantly commoner among men than it was among women but that since 1940 the incidence of acute myocardial infarction among women has been similar to that among men. In the current study the entire autopsy series was divided into diabetic and nondiabetic men and women and the incidence of acute myocardial infarction was determined for each sex in each group (diabetic and nondiabetic) and for each period (before and after 1940). The results thus obtained indicate that in this autopsy series since 1940, acute myocardial infarction is significantly commoner among diabetic women than among diabetic men; whereas, the incidence is still significantly greater among nondiabetic men than among nondiabetic women.

Various other clinical and anatomical characteristics of diabetics with acute myocardial infarction and nondiabetics with

acute myocardial infarction are compared in this study, and most characteristics are found to be similar.

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THE TREATMENT OF INTESTINAL PARASITIC INFECTIONS

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Introduction

THE PAST 10 years have seen the development of a number of new drugs effective in the treatment of intestinal parasitoses, including particularly several amebicidal drugs and piperazine preparations used in ascariasis and enterobiasis. Nevertheless, improved results in antiparasitic therapy have been due as much to a better understanding of the principles of diagnosis and appreciation of the natural history of the infections as to the use of new therapeutic agents.

Diagnostic methods have been measurably improved in amebiasis. First of all two old myths have been dispelled. Proctoscopy has been shown to be less dependable than adequate stool examination,[1] and the unreliability of distinguishing the active stage of Entamoeba histolytica from that of other amebas on the basis of motility alone is now acknowledged and widely known. New methods for preserving stool specimens make it possible for patients to be diagnosed and treated at a distance from the physician's office.* Improvement in diagnostics together with an increased awareness of the ease of reinfection have reduced the incidence of "refractory" amebiasis and at the same time the duration of the effective course of treatment.

While techniques for the quantitative estimation of worm burden have long been used in the management of intestinal helminthic infections, because of its convenience the direct smear method[4] allows the physician to perform routine egg counts if he desires them. In this way he is better able to judge the role of hookworm infection as a cause of anemia or of trichocephaliasis as a cause of diarrhea; to forego treatment in asymptomatic light infections, and the better to estimate the efficiency of the treatment. In enterobiasis, in which egg-count methods are not applicable, the use of serial cellulose adhesive anal impressions ("swabs") has served much the same purpose.[5]

In the management of parasitoses, just as of bacterial infections, the physician must contend not only with the parasite but also with the disease resulting from its presence or due to supervening causes. In some instances measures directed against the infection may be postponed until the patient's condition is improved; in others immediate antiparasitic treatment is indicated, and in still others the parasitic infection may be ignored. This paper is concerned with the management of those infections of the human intestine due to animal parasites likely to be encountered in the continental United States. For each parasite consideration is paid to principles of diagnosis necessary for proper management and to treatment of the patient as well as the infection.

Protozoan Infections

Amebiasis

The management of dysenteric and nondysenteric amebiasis differs so widely that the two types of disease will be considered separately.[6]

Amebic Dysentery.—In amebic dysentery the clinical and sigmoidoscopic pictures are usually characteristic, and the stools almost invariably contain trophozoites of Entamoeba histolytica. Diagnosis is therefore comparatively easy.

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The management of amebic dysentery depends on its severity. If very frequent stools containing bloody mucus are being passed, it is advisable to confine the patient to bed. Blood and fluid levels must be restored, by transfusion or infusion if necessary. If abdominal cramps and tenesmus are very severe, it is advisable to quiet the patient by hypodermic administration of opiates. Demulcent agents such as bismuth subnitrate or bismuth subcarbonate are of limited value but may provide partial relief pending the administration of more effective drugs. The average patient requires none of the above. Although he may be fatigued both physically and mentally by tenesmus and frequent stools, he appears relatively well.

Since the occurrence of amebic dysentery may be related to the presence of nutritional deficiencies,† a nutritious bland diet, rich in protein and vitamins, should be provided.

Unfortunately the best of the amebicidal drugs are less effective when dysentery is present. The primary objective of the physician is to obtain immediate relief from the dysentery. Many antibacterial agents including both antibiotics and sulfonamides are able to check amebic dysentery,‡ although some are relatively ineffective in eradicating the infection. Of these, oxytetracycline, chlortetracycline, and erythromycin are the most efficacious. Erythromycin is preferable, since it alters the intestinal flora less than the tetracyclines and removes nonpathogenic amebas as well as E. histolytica.[12] It is administered in the amount of 0.5 gm. every eight hours for five to seven days. Usually dysentery will cease within 48 hours, although this does not mean that the infection has been eradicated.

An amebicidal drug of low solubility and established potency is given concurrently with the antibiotic. The purpose is not to check the dysentery but to eradicate the infection when normal rates of peristalsis and mucus flow have been established. Glycobiarsol (Milibis) is used routinely at the Tulane Tropical Medicine Clinic because of its high efficacy,[13] short course of therapy, and the intermediate cost and toxicity. It is administered in the amount of 0.5 gm. three times a day for eight days. Persons reacting unfavorably to glycobiarsol (an arsenical) may be given diiodohydroxyquin (Diodoquin), 650 mg. three times a day for 21 days, or fumagillin (Fumidil), 10 to 20 mg. three times a day for seven days.[14] Diiodohydroxyquin is virtually without toxic effect. Fumagillin may produce gastrointestinal disturbances or allergic dermatitis and rarely leucopenia.

If a reasonable period of trial with erythromycin or other antibiotic fails to control the dysentery one must resort to emetine. Emetine hydrochloride is a drug of dramatic efficacy in relieving the dysentery of amebic colitis but may have such toxic effects on the patient's myocardium, skeletal musculature, and nerves that precautions must be taken to avoid serious complications. Hospitalization is recommended. The patient should be at complete bed rest through the period of emetine therapy and for a few days thereafter. Flattening and inversions of the T waves are expected changes and are per se no cause for alarm. Premature beats, slurring and notching of QRS complexes in a single lead, and prolongations of P-R intervals not over 0.20 of a second are significant changes but do not require withdrawal of emetine. Widening of QRS complexes and prolongation of the P-R interval to 0.21 or more of a second may require cessation of emetine therapy. Increase in pulse rate and drop in blood pressure are additional warning signs of dangerous myocardial poisoning. Sometimes the drug causes muscular weakness or neuritis. In any case the decision to stop emetine is dependent on the clinician's evaluation of the patient's need for the drug and physical as well as ECG evidences of intoxication.[15]

Since emetine is a cumulative poison, it is given no longer than is required to stop the dysentery and for not more than five

† References 7 and 8.

‡ References 9-12.

days in the absence of extraintestinal amebiasis or ameboma. The dose is 1 mg. of emetine hydrochloride per kilogram of body weight, but never in excess of 65 mg., in deep subcutaneous injection once a day or in two divided daily doses. Emetine should not be expected to eradicate amebic colitis but will usually reestablish normal stools within five and frequently within two days.[6]

In all cases of intestinal amebiasis chloroquine should be given prophylactically against amebic infection of the liver. It may be prescribed from the beginning of therapy or after the dysentery has been checked. Its action against intestinal infection is slight. The dose is 0.5 gm. of chloroquine phosphate (Aralen) twice daily for two days, then 0.25 gm. twice daily for 21 days.

Nondysenteric Amebiasis.—In nondysenteric amebic colitis diagnosis is dependent on demonstration of the amebas. Since these patients do not require emergency treatment, the first phase of management consists in establishing the diagnosis. The patient is requested to bring in three normally passed stools on successive or alternate days. If these are all negative he then provides a liquid stool following saline purgation. (Disodium acid phosphate and sodium sulfate purgation are reportedly superior to magnesium sulfate for this purpose.) If this is also negative, sigmoidoscopy is carried out. In preparation for this procedure a saline purgative is taken the previous night, and two hours preceding the examination the lower bowel is cleansed with normal saline enemas. During sigmoidoscopy the bowel is examined for ulceration and material is aspirated preferably from the ulcers, if any, and searched immediately for parasites. The diagnosis of amebiasis is not established unless typical trophozoites or cysts of E. histolytica are recognized in stool specimens or sigmoidoscopic aspirate.

The drugs employed in the Tulane Tropical Medicine Clinic for nondysenteric amebiasis are glycobiarsol, diiodohydroxyquin,[13] and fumagillin,[14] as described above. The tetracycline antibiotics or erythromycin are also effective but do not present sufficient advantages in nondysenteric amebiasis to warrant their excessive cost and the risk of developing strains of resistant bacteria.

Chloroquine is given as a prophylactic against hepatic involvement as outlined above for dysenteric amebiasis.

Presumptive Amebiasis.—Not infrequently the physician is justified in making a presumptive diagnosis of amebiasis even though the etiologic agent has not been demonstrated. In such instances treatment will be as outlined above, but satisfactory response to therapy should not be accepted as proof of the diagnosis, which remains only presumptive. Caution must be exercised so that some other disease may not be overlooked.

Certain atypical features may be produced in intestinal amebiasis. These include abundant pus in the stools, massive intestinal hemorrhage, and colonic masses palpable or demonstrable by x-ray. Following antiamebic therapy, patients presenting these findings, even though the diagnosis of amebiasis was proved, deserve investigation for concomitant disease, particularly carcinoma and ideopathic ulcerative colitis.

Refractory Amebiasis.—Although refractory intestinal amebiasis may occur under certain circumstances, *viz.*, highly resistant strain of the ameba, an abnormally susceptible host, nutritional deficiencies, coexistent intestinal disease of other etiology, such cases are infrequent in this country. When most alleged instances of resistance are subjected to critical scrutiny it is found that the diagnosis of amebiasis is entirely erroneous or that reinfection has occurred. If an amebic infection does not respond to standard therapy the physician should attempt to corroborate the diagnosis at another laboratory. If he finds that he is indeed dealing with amebiasis, the other members of the patient's family, as well as other possible sources of reinfection such as contaminated food or polluted water, must be tested. Infected contacts should be recom-

mended for treatment and faults in group hygiene or sanitation corrected.

In the bona fide case of resistance, provision of a nutritious bland diet, vitamins, and simultaneous administration of broad-spectrum antibiotics with glycobiarsol or diiodohydroxyquin will produce eventual cure.

Nonpathogenic Amebiasis.—In certain instances treatment is indicated for intestinal amebas other than E. histolytica in case only these nonpathogenic amebas have been demonstrated. This may occur when an abundance of nonpathogenic amebas may interfere with adequate examination for E. histolytica. Glycobiarsol, diiodohydroxyquin, erythromycin, and fumagillin all are usually capable of eradicating the nonpathogenic amebas as well as E. histolytica.§

Ameboma.—When a patient has a colonic mass as well as E. histolytica in his stool the physician must distinguish an ameboma from carcinoma. Surgical exploration must be postponed until after chemotherapy, but if the lesion is low enough it may be biopsied sigmoidoscopically. Emetine hydrochloride is administered by subcutaneous injection (1 mg. per kilogram of body weight per day for 10 days but not over 65 mg. in one day). Within this period an ameboma will show definite decrease in size but carcinoma will not. Following the course of emetine, curative amebicidal therapy is given. If a mass still remains exploration may be done, since an ameboma and carcinoma may exist together.[16]

Follow-up.—In any case of amebiasis several stools should be examined after therapy to detect relapse or reinfection. Ordinarily three stool examinations within 10 days following completion of therapy are considered sufficient. Obviously the more prolonged the period of follow-up, the greater is the reliability of negative stools and likewise the greater is the possibility of detecting a reinfection.

§ References 12 and 13.

Giardiasis

Giardiasis, caused by the flagellate Giardia lamblia colonizing in the duodenum and gall bladder, is a frequent asymptomatic infection, but in some instances may cause diarrhea or upper abdominal discomfort. If stools from patients suspected of having giardiasis are negative, duodenal and gall bladder aspirates should be obtained and examined for the parasite.

Because this protozoon may act as a pathogen, treatment of the infection is advisable, since therapy is cheap, nontoxic, and highly effective. This consists in administration of quinacrine (Atabrine) hydrochloride, 0.1 gm. three times daily for five days.

Balantidiasis

Balantidiasis is infection of the large intestine with the ciliate Balantidium coli. The lesions produced and symptomatology are similar to those of advanced amebic dysentery except that the ulcers are typically larger and do not have undermined edges. Secondary bacterial infection tends to be more pronounced than in early amebic colitis, so that purulent as well as bloody mucus may be passed.

The usual host for this parasite is the pig. Human infections ordinarily are sporadic and occur under the most unhygienic conditions, in which human beings may ingest material contaminated with pig feces. However, the disease may be transmitted from person to person, once the porcine strain has become well adapted to the human host. Frequently supervening disease of a debilitating nature, such as a nutritional deficiency, or one damaging to the colon like trichocephaliasis, coexist with balantidiasis. The balantidial infection may disappear without specific therapy when such contributory factors are corrected.

Balantidiasis has been successfully treated with carbarsone, but oxytetracycline is preferable. The latter is administered in the amount of 1.5 to 2.0 gm. daily in three divided doses for 10 days.[17] Erythromycin and fumagillin have been found ineffective

in balantidial dysentery.[12] Wherever human balantidiasis is demonstrated, efforts should be made to improve the environmental sanitation of the patient.

Nematode Infections

Trichinosis

Trichinosis, caused by Trichinella spiralis, is largely a systemic rather than an intestinal infection, but adult female parasites, the source of the disease-producing larvae, reside in the intestinal mucosa for as long as six weeks after inoculation. Usually by the time diagnosis is made opportunity for treatment of the intestinal infection has passed. If trichinosis is suspected early in the disease on the basis of an "acute food poisoning" episode following consumption of inadequately cooked pork, several saline purges with sodium sulfate may dislodge the parasites before they become established.[18]

Experimental studies indicate that piperazine citrate given in a daily dose of 2 to 3 gm. for seven days may remove many of the adult worms.[19] Since this drug is well tolerated, it is worthy of trial. Neither purgation nor piperazine will effect the larvae once they are distributed throughout the body.

Trichuriasis

Light infections with the whipworm Trichuris trichiura are mostly confined to the cecal region and adjacent ascending colon. Damage to the bowel may be practically negligible and the patient asymptomatic. With heavier infections worms are found throughout the entire colon, a severe colitis is produced, and the patient is troubled with a chronic dysentery.[20] Proctoscopy in these patients reveals a beefy red friable bowel with attached worms. Patients suffer severely from heavy infections if the worms are not removed.

All methods of treatment are more effective in heavier infections than in light ones. Since the latter are relatively harmless and generally refractory, there is usually little or no indication for treating them. Heavy symptomatic infections may be converted by treatment into light asymptomatic ones.

Egg counts should be made on all patients with whipworm infection. If there are more than 25 eggs per milligram of feces, treatment should be carried out as outlined below. If dysentery is present even though the number of eggs is low, the infection may consist largely of sexually immature worms. This may be verified by proctoscopy, which will reveal attached worms which are transparent and smaller than sexually mature ones.

The most effective treatment in massive whipworm infection is by hexylresorcinol enemas. Cleansing enemas are given preliminarily up to three in number. The buttocks, thighs, and perineal and genital regions are coated with petrolatum to prevent burning of the skin by returned or spilled material. A retention enema consisting of 400 to 500 ml. of 0.2% hexylresorcinol suspension heated to body temperature is given slowly. This is retained 30 minutes and return is encouraged if necessary after one hour by an additional tapwater enema.[21]

A single treatment may suffice, but if sigmoidoscopy and stool examinations made two days after treatment indicate failure or only partial success, the treatment may be repeated on the third day. Attempts to eradicate all of the worms by repeated treatments do not benefit the patient and subject him to an unnecessary ordeal.

The most effective oral medication is leche de higuerón, the fresh, unpreserved sap of a tree of the fig family in the American tropics, which is administered in a single dose of 60 ml.[22] This crude drug is not available in the United States. Treatment with a mixture of tetrachlorethylene and chenopodium oil sometimes removes many worms but cannot be depended upon for consistently good results or complete eradication of the parasites.

Ferric and ammonium citrate in a dose of 6 to 12 gm. daily not only helps to correct the microcytic anemia commonly seen

in this infection but also removes some worms.[23] Although it is not a very efficient anthelmintic, its low cost and low toxicity together with its hematinic effect make it a useful drug for outpatients.

Ascariasis

Ascariasis is caused by Ascaris lumbricoides, which lives in the small intestine. Since the infection may be completely eradicated, and since a single worm can produce serious illness by migration into abnormal sites, every case of infection should be treated. Diagnosis is by microscopic demonstration of the eggs in fecal smears.

Uncomplicated Intestinal Ascariasis.—Piperazine hexahydrate and closely related piperazine compounds are the best drugs for treatment of intestinal ascariasis because of their low toxicity, relative efficiency, and moderate cost.[24] Although the optimum dosage has not been established, the writers have had excellent results employing syrup of piperazine citrate in the amount of 5 to 10 ml. three times daily for seven days (each ml. containing 100 mg. of piperazine hexahydrate). The worms are usually passed on the second and third days of treatment.

Failure of treatment as indicated by persistence of eggs in the stool after treatment calls for repetition of the course or administration of hexylresorcinol crystoids after overnight fasting. This drug is given in a single dose of from 0.6 gm. for infants to 1.0 gm. for adults. The pills must be swallowed whole without chewing.[18]

Purgation is not necessary with either piperazine or hexylresorcinol therapy.

Complicated Intestinal Ascariasis.—The principal complications of ascariasis are surgical and include the following in order of frequency: intestinal obstruction, intestinal perforation, invasion of the common bile duct with production of obstructive jaundice or liver abscess, appendicitis, and volvulus. All but the first are managed surgically and will not be discussed in this article.[25]

Intestinal obstruction due to ascariasis is commonest in children between the ages of 1 and 4 years. The history is usually one of a febrile illness, during which the child begins to vomit and pass ascarides. Vomiting becomes more frequent, bowel movements cease, the abdomen becomes distended, and the child becomes critically ill. In addition to the usual signs of intestinal obstruction, a bolus of worms may be palpable, most often in the right lower abdominal quadrant.

These children are to be admitted to a hospital and prepared for surgery. The nature of the precipitating febrile illness is determined, if possible, and treated appropriately. This is usually an upper respiratory infection, pneumonia, or otitis media. If the etiology of the precipitating illness is not identifiable, administration of penicillin or in sensitive patients a broad-spectrum antibiotic is advisable. Antipyretic measures such as alcohol rubs and ice bags may be used to minimize the fever. Fluid is restored by intravenous infusion. Similar physiologic solutions instilled by proctoclysis not only restore fluid but stimulate peristalsis.

In most cases by the time the patient is adequately prepared to withstand surgery the necessity for surgery has disappeared. The worms disengage themselves from the bolus and are either passed into the colon or redistribute themselves in the small intestine. Patients whose obstructions persist must be operated on, and the worms must be removed.

As soon as peristalsis is reestablished, whether surgery has been performed or not, treatment as for uncomplicated intestinal ascariasis may be carried out.

Since the same child may have not only repeated infection with Ascaris but also repeated surgical complications of the infection, long-term follow-up stool examinations at one- or two-monthly intervals are advisable to detect reinfection. Stools may contain eggs again within three months after returning to a contaminated environment following successful treatment.

Enterobiasis (Oxyuriasis)

Enterobiasis is infection of the colon with Enterobius vermicularis, the commonest helminthic infection of adults and children in the United States. It is particularly prone to produce reinfection, and management of a case must take into consideration severity of infection and impermanence of cure.

Before treatment it is desirable to confirm the diagnosis and estimate the severity of infection by making a series of cellophane adhesive tape anal impressions on several (preferably seven) successive days. The severity of infection and likelihood of reinfection are roughly proportional to the percentage of positive tests in a week's series.[5] Light infections need not be treated unless they are symptomatic or are an important source of reinfection for other persons. In symptomatic light infections a special effort should be made to locate the source, often another member of the same household and usually a child who is heavily infected, though not necessarily symptomatic. Treatment of an entire household will sometimes prevent reinfection, but this cannot be expected when children are exposed to reinfection in heavily contaminated environments at school or play.

Piperazine and methylrosaniline chloride medicinal are both effective in enterobiasis, probably equally so. Piperazine is preferred because of lack of side-effects and ease of administration.|| The dose is 5 to 10 ml. of syrup of piperazine citrate three times daily for 10 to 14 days. Methylrosaniline chloride medicinal is given in tablets with an enteric coating made to dissolve in four hours. The dose is 1 grain (60 mg.) three times daily one hour before meals for one week. (For children the daily dosage is 10 mg. per year of apparent age.)

Certain hygienic measures help in reducing the likelihood and degree of reinfection. These include closed sleeping garments for small children so that their fingers will not come in direct contact with the perineum; washing undergarments and bedclothes in hot water daily; trimming of fingernails; meticulous cleanliness of the fingers.

Following treatment perianal impressions are again made daily for a week, and those patients with seven negative tests are assumed to be cured.

Hookworm Infection

Necator americanus and Ancylostoma duodenale, the hookworms commonly infecting human beings, live attached to the lining of the small intestine and suck blood. Hookworm disease is an iron-deficiency anemia due to chronic blood loss. It develops when the number of hookworms in the intestine is so large that daily blood loss exceeds the amount that is replaceable by the hematopoietic system. Just as in whipworm infection, in hookworm infection the occurrence and severity of the disease are related to the worm burden. Like Trichuris, the last few hookworms are very difficult to eliminate, and in most cases repeated anthelmintic therapy directed against a minimal hookworm infection is not likely to benefit the patient.

Tetrachloroethylene is still the most effective drug against human hookworm infection. Under proper management it is essentially nontoxic. To be effective it must be fresh. It is given in soft gelatin capsules in the morning after an overnight fast. The dose is 0.06 ml. per pound of body weight, with a maximum dose of 5.0 ml. Most satisfactory results are possibly obtained when no pre- or post-treatment purgative is given.[28]

In hookworm disease the anemia and hypoproteinemia must be treated. In the most severely ill patients blood transfusion is indicated, but in a majority administration of iron, high protein, high caloric diets, and supplementary vitamins will suffice. In cachectic persons or those with severe heart or liver disease administration of tetrachloroethylene should be postponed until the patient's condition is improved. Meanwhile a preliminary attack on the parasitic infec-

|| References 26 and 27.

tion can be made with hexylresorcinol crystoids, 0.6 to 1.0 gm., repeated at intervals of two to four days. No pre- or post-treatment purge is necessary.

Strongyloidiasis

Strongyloides stercoralis, the causative agent of strongyloidiasis, is a delicate nematode which parasitizes the human small intestine, provoking duodenitis and jejunitis, occasionally ileitis and colitis, and causing various gastrointestinal symptoms.[29] As in giardiasis, diagnosis may require examination of duodenal aspirates as well as feces to obtain evidence of the parasite. Results of treatment may be evaluated not only by improvement in symptoms and decrease in number of larvae in the stool or duodenal juice, but also by decrease in the number of circulating eosinophiles and improvement in the appearance of the duodenum as seen on x-ray.

There is still no adequate therapy for intestinal strongyloidiasis. Methylrosaniline chloride medicinal is the only effective drug. It is given orally in enteric-coated tablets timed to liberate the drug in 90 minutes. A four-day course has been found most effective. On the first day 1 grain (60 mg.) is given three times one hour before meals, and the dose is increased by 30 mg. each day so that on the fourth day the patient receives 150 mg. three times. If vomiting occurs the medication is discontinued, at least temporarily.

Some cures may be obtained by administering methylrosaniline chloride medicinal (25 ml. of 1% aqueous solution) by duodenal catheter.[18] In the writers' experience intravenous administration of methylrosaniline chloride has not been found satisfactory and has produced unpleasant side-effects.

In order to minimize the danger of hyperinfection (development and migration of larvae produced by internal autoinfection), constipation should be avoided, the perianal skin should be cleansed after defecation, and clothing soiled with even a small amount of feces should not be worn.

Tapeworm Infections

In the United States several species of tapeworms may infect the human intestine. They include Taenia saginata, T. solium (rarely acquired in the United States), Hymenolepis nana, H. diminuta, Dipylidium caninum and Diphyllobothrium latum. Of these, infection with T. saginata, T. solium, and D. latum results from eating improperly cooked beef, pork, and fresh-water fish, respectively; these tapeworms are usually found in adult persons. Infection with H. diminuta or D. caninum is acquired accidentally by ingesting fleas (or certain beetles in the case of H. diminuta) which harbor the larval stage of the worms, and H. nana infection is usually acquired by direct person to person transfer. The latter three species are found primarily in children or in institutions for the insane.[18]

Of the six intestinal tapeworms listed above, T. saginata, T. solium, H. nana, and D. latum have the potentiality of producing serious intestinal disease. T. solium also causes cysticercosis, with seeding of larval worms throughout the extraintestinal viscera, H. nana occasionally produces allergic reactions, and D. latum rarely a macrocytic anemia.

Modern treatment for all intestinal tapeworm infections is the same, *viz.*, with quinacrine hydrochloride. Quinacrine treatment is as follows:

The patient receives a milk diet for one day. That evening a purgative is given—customarily an ounce (30 cc.) of castor oil. This serves not only to clear the bowel but also to aid in fixing the dose for post-treatment purgation. The following morning breakfast is withheld and a cleansing enema is given. Quinacrine hydrochloride, 0.8 gm. (8 tablets), is administered in one dose. One hour later one ounce or more of castor oil is given, depending on response to the previous night's dose. Quinacrine may provoke a disagreeable gastritis which interferes with success of the treatment if there is much vomiting. This may be lessened by

giving sodium bicarbonate with the quinacrine.[30]

Infections with H. nana are usually multiple, and the worms passed after treatment may be so damaged as to be unrecognizable. To test the success of therapy one must therefore examine the stool for eggs for two to three weeks thereafter.

Following treatment for other tapeworm infections all liquid stools must be collected and examined. If the worm has been passed intact the head will be found readily at the slender end, but if the scolex is detached from the remainder of the worm the stool should be washed carefully by sedimentation and the sediment thoroughly searched for the scolex. Failure to find the scolex does not necessarily indicate failure of the therapy; the patient should be observed for three to four months after treatment. He should not be subjected to a repetition of treatment unless he resumes passing eggs or proglottids.

Schistosomiasis

Schistosomiasis is not indigenous to the continental United States, but many North American physicians encounter this infection in increasing numbers of Puerto Ricans harboring the parasite who have migrated to several of our large cities. Manson's schistosomiasis, caused by Schistosoma mansoni, is the type of the disease occurring in the New World. Oriental intestinal schistosomiasis, caused by S. japonicum, and vesical schistosomiasis, by S. haematobium, though important in other parts of the world, are infrequently seen in the United States.

Diagnosis of Manson's infection is made primarily by demonstration of the eggs in feces or in tissue obtained by rectal biopsy. Certain immunologic tests are also helpful.

The most effective drug in the treatment of schistosomiasis is antimony potassium tartrate. A freshly prepared 0.5% solution in 5% dextrose or isotonic saline solution is given very slowly by the intravenous route on alternate days. The adult dose the first day is 8 ml. (0.04 gm. of antimony potassium tartrate), and the amount is increased by 4 ml. (0.02 gm.) each administration until an individual dose of 28 ml. (0.14 gm.) is reached. The entire course consists of 18 injections totalling 444 ml. (2.2 gm.).¶

For children antimony potassium tartrate may be given by reducing the dose according to body weight, but so much difficulty is encountered with venous thrombosis and cellulitis due to extravasation of the drug that a different route of administration is preferable. Stibophen (Fuadin) which is administered intramuscularly is therefore preferred in the treatment of children, even though it provides a lower cure rate than does antimony potassium tartrate. Initially 0.5 ml. of a 6% solution is given intragluteally. The amount is increased stepwise to 3.5 ml., which is continued on alternate days until 15 to 25 ml. has been given.[31]

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Case Reports

SENSITIZATION AND SUBSEQUENT DESENSITIZATION TO PROBENECID (BENEMID)

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PROBENECID (Benemid)* has been established as an outstanding uricosuric agent of value in the treatment of chronic gout.† The drug has been shown to control hyperuricemia, to cause the diminution in size and even disappearance of tophi, to cause the resolution and repair of bony destructive lesions of gout, to reduce the incidence of acute attacks of gout in the course of the chronic disease, and to increase the sense of well-being in the gouty subject. Indeed, the drug has been called "the insulin of gout"‡ and has been declared to be "the most significant advance in the treatment of gout in many years."§ Accordingly, the sensitization of a patient to probenecid represents a loss of these potential benefits, especially to the patient who has seen his gout improve even to the point of disappearance of tophi, and it is a loss to which the patient can reconcile himself only with great difficulty.

It was under these very circumstances that the following study was undertaken, and the successful desensitization of a patient previously sensitized to probenecid is reported here for the first time.

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* Benemid is the trademark of Merck & Co., Inc., under which probenecid, *p*-(dipropylsulfamyl) benzoic acid, is supplied.

The probenecid as pure chemical was supplied by Merck & Co., Inc.

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‡ Bartels, E. C.: Personal communication to the authors.

§ Thorn, G. W.: Personal communication to the authors.

Report of Case

In February, 1951, a 65-year-old man, the victim of chronic tophaceous gout, the clinical course of which was punctuated by recurrent, acute episodes, received 2.0 gm. of probenecid daily for 10 days and thereafter 1.0 gm. for an additional 20 days, a total of 40 gm. of the drug over a period of 1 month. The medication gave rise to no recognizable symptoms, and it was then discontinued, as it was without evident therapeutic effect.

Approximately 10 months later, in December, 1952, when treatment with the drug was reinstituted, within approximately 30 minutes after the ingestion of a single dose of 0.5 gm. of the drug there developed marked itching of the feet, swelling of the face and scalp, and giant generalized urticaria. Shortly thereafter there was profuse sweating, faintness, pallor, tachycardia, and a marked fall of blood pressure. Following the administration of tripelennamine, the foregoing signs subsided gradually in the course of the night, but a moderate febrile reaction persisted for approximately 24 hours.

Despite the foregoing alarming episode, the clinical course of the gout in this patient and the reports of the beneficial effect of probenecid upon gout were such that the temptation grew strong to attempt desensitization of the patient to the drug. The potential hazard of attempting to do so was recognized. It was natural to speculate whether excipients utilized in the manufacture of the commercial tablet of the drug could be at fault or whether the probenecid itself was the sensitizing agent. Accordingly, the pure chemical was obtained and used for the desensitization program.

Inasmuch as little precise knowledge concerning the ability to desensitize a host with a pure chemical substance was available, and because of the violent systemic response that had followed the ingestion of the drug, attempts at desensitization were made most cautiously. The initial oral dose was approximately 2 minims (0.12 cc.) of an aqueous solution of probenecid that contained 5γ per cubic centimeter, and on each succeeding day thereafter the dose administered was increased in amounts of from 1 to 3γ until 15γ was given.

Thereafter the increments were from 5 to 20γ until the dose was 150γ in a day, after which this was increased daily by 250γ until a dose of 2 mg. was reached. When after 38 days the daily administration was 15 mg., that amount was kept fixed for 10 days because of recurring mild urticaria, and for one day the amount administered was reduced to 7.5 mg. That the patient was sensitive to the chemical itself and not to some excipient in commercial tablets was thus confirmed. Thereafter the administration of the drug in encapsulated form was increased 5 mg. a day until a dose of 75 mg. was reached, and then the rate of increase was approximately 10% daily until, 99 days after the procedure was initiated, 2 gm. was given daily (Table).

The beneficial effects of the treatment with probenecid did not occur rapidly enough to be called "dramatic," and during treatment two small pea-sized nodules appeared on the extensor tendon of the right ring finger that were indistinguishable clinically from soft-tissue tophi,‖ but the treatment resulted in (*a*) control of the hyperuricemia, (*b*) diminution in the size of tophi, (*c*) the disappearance of some established tophi, and (*d*) a lessened number of acute attacks of gout during a period of approximately one and one-half years.

The foregoing case record describes an exceptional reaction to the drug probenecid and records the successful desensitization of a patient with a pure chemical substance.

Dosage Schedule

Days of Therapy	Dosage Form	Daily Increment	Increase of Probenecid		Days Required
			From	To	
1–6	Solution, 5 γ/ml.	1–3 γ	1 γ	5 γ	6
7–16	Solution, 5 γ/ml.	2.5–20 γ	5 γ	150 γ	10
17–33	Solution, 250 γ/ml.	150–250 γ	150 γ	2 mg.	17
34–38	Solution, 250 γ/ml.	1,000–7,500 γ	2 mg.	15 mg.	5
39–49	Capsule, 5 mg.	Period of constant dosage at 15 mg./day because of sensitivity phenomena—mild urticaria and itching			11
50–61	Capsule, 5–25 mg.	5 mg.	15 mg. (0.015 gm.)	75 mg. (0.075 gm.)	12
62–99	Capsule, 50 mg.–0.5 gm.	Then average of 10% of preceding daily dose	75 mg. (0.075 gm.)	2,000 mg. (2.0 gm.)	38
					99

That the pure probenecid was responsible for the manifestations of a state of specific sensitivity was evidenced by the development of pruritus and of urticaria on several occasions during the foregoing period and by the subsequent development during treatment with the drug of a mild dermatosis and of recurrent pruritus.

During the time in which probenecid has been administered, the patient adhered to a low-purine diet, supplemented by alkalinization of the urine during the initial months of full therapy and by the daily administration of 1.0 or 1.5 mg. of colchicine, with increased dosage of the latter drug when acute episodes occurred, as they did six times in as many months. Hydrocortisone in small doses (10 to 40 mg. a day) was taken likewise for four months to help relieve the chronic arthritis and pruritus, and in its stead prednisone was substituted when it became available, starting with 40 mg. a day and reducing gradually to a maintenance dose of 10 mg. daily by the end of nine weeks.

Comment

Probenecid was introduced into human medicine on July 22, 1949,[7] for the purpose of enhancing the concentration of penicillin in the plasma, a use which the drug continues to enjoy. Only later, following the lead established by the studies showing that a related compound, carinamide, had uricosuric effects,[8] was it discovered that probenecid was an even more potent uricosuric agent.¶ Subsequent investigations have demonstrated uniformly the prompt and sustained serum-uric-acid-lowering effect of probenecid. Although the

‖ These nodules have subsequently disappeared.

¶ References 1-3.

administration of salicylates in large daily doses, 5 gm. and more per day, has been shown to have striking uricosuric effects and even to have resulted in the dissolution of a destructive lesion of tophaceous gout,[9] the symptoms of salicylism are too distressing to the majority of patients to permit long continuance of such therapy. Contrariwise, probenecid has been administered continuously for periods up to five years, in daily doses ranging between 0.5 and 2 gm. per day, with a minimum of side-effects.

In 1955 the side-effects of probenecid therapy in 2502 patients were reviewed.[10] This number of patients was drawn from the experiences of the authors, from the medical literature, and from personal communications from many colleagues. In this paper the authors invited correspondence from any reader who had encountered toxicity in connection with his use of probenecid. The small number of responses can be variously interpreted: as due to a disinclination of physicians to report their experiences, to the insignificance of the side-effects observed, or to an actual paucity of patients showing side-effects in connection with the administration of the drug. In the light of the foregoing facts, the authors have seen no reason to alter the statements that were presented originally by them.

However, sensitization to probenecid does occur in a few persons, 1% to 2%. In the majority of such persons it has been determined that they manifested sensitivity to other commonly employed medications or that probenecid had been administered "intermittently." In the earlier phases of the investigation of probenecid in the treatment of gout, some investigators expressed themselves as favoring "intermittent" administration. It was argued that it was unnecessary to give therapy continuously after the uric acid pool had been reduced to normal or to near-normal levels and the serum uric acid had been maintained within the normal range for a period of months and, secondly, that the continued administration of probenecid invited the possibility that the uricosuric effect might diminish or even disappear due to the development of tolerance to the drug. The consensus of recent experience favors the uninterrupted, continuous administration of probenecid and hence the appropriateness of the designation of it as the "insulin of gout."

The decision to institute probenecid therapy rests upon a definitive diagnosis of gout. The criteria by which such a diagnosis is established may differ somewhat, but a familial history, hyperuricemia of 6 mg/100 ml. or more, and one or more classical attacks of acute gout relieved by colchicine, leave little room for doubt. It is suggested that the earlier a definitive diagnosis of gout can be made the more imperative it is that probenecid therapy be instituted. Gout has never been shown to reverse its course spontaneously. Normal kidneys are unable to excrete those excesses of uric acid which are synthesized within the body of the gouty person, and, except for that small amount of uric acid which is metabolized, the excess of uric acid is, by definition, deposited in the tissues of the patient. The joints, the tendons, ligaments, bursae, cartilages, the kidneys, and, to a lower degree, the myocardium are vulnerable to uric acid deposits. It seems only reasonable that an agent of low toxicity that can strike the balance between the overproduction or the subnormal destruction of uric acid by the gouty subject and the excretion of it into the urine and that by demonstration can maintain the uric acid pool and serum uric acid at near-normal levels should be employed as a safeguard against the otherwise irreversible damage that may result from deposition of urates in the tissues. Apart from a single, seemingly unique, success with salicylates,[9] the healing of a destructive bony lesion due to gout had never been reported prior to that following the administration of probenecid to a patient for 18 months.[6]

The foregoing serves only to emphasize

the potential seriousness of the loss to a patient suffering from gout who becomes sensitized to probenecid. The case here reported demonstrates that a patient who suffered a severe reaction due to sensitivity to the drug was successfully desensitized and presently continues on full probenecid therapy. The fact that the patient was sensitive to probenecid seems firmly established by the severity of the reaction following the second administration of the drug after an interval of 10 months without the drug and the reappearance of mild symptoms of urticaria and itching at the 15 mg/day stage of the desensitization program. The success of the continued therapy with probenecid after desensitization is attested to by the control of hyperuricemia, the disappearance of some established tophi, the diminished size of others, the reduction in frequency of acute gouty attacks, and the continued sense of well-being of this patient.

The exact nature of the "nodules" which appeared and subsequently disappeared during probenecid therapy, in the face of the foregoing evidences of good control of gout, is not clear. The explanation that these nodules were "abnormal tophi" is scarcely tenable. That these nodules may be "fibrous," as frequently seen in rheumatic fever and in those who have the rheumatoid diathasis, may be considered. One is reminded of various "collagen disease syndromes" that have been reported under similar circumstances. The patient reported here is being kept under close observation, and an explanation of the nodules may be forthcoming. No eosinophilia has been observed in the peripheral blood. That the patient reported here was exquisitely sensitive to probenecid has been established, and it can be theorized that it is unwise to administer a drug on a continuing basis to a person who has once been shown to be sensitive to the agent in question. Nevertheless, continuation of therapy after desensitization to probenecid has offered this patient comfort and control of his gout that was not otherwise obtainable.

Summary and Conclusions

A patient whose sensitivity to probenecid (Benemid) was thoroughly established has been desensitized by the administration of small daily increments of it during a period of 99 days. Subsequent to desensitization the patient was able to take full probenecid dosage with the expected benefits of such treatment: control of hyperuricemia, the diminution and disappearance of established tophi, a decreased incidence of acute gouty attacks, and an increased sense of well-being.

Desensitization of a patient to the pure chemical, probenecid, is reported here for the first time. The suggestion is made that for those rare gouty patients shown to be sensitive to probenecid and for whom the proved benefits of treatment with the drug offer promise of rehabilitation, a program of desensitization may be undertaken with the hope of enabling the patient to take the drug once again.

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LOEFFLER'S SYNDROME WITH CARDIAC INVOLVEMENT

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LOEFFLER first reported five cases of transient pulmonary infiltration associated with eosinophilia in 1932.[1] The occurrence of cardiac involvement with pulmonary infiltrations and eosinophilia has been reported in one case of Mark [2] and in the case of Schwartz.[3] Mark's case had an extensive infiltration throughout the left lung. A bronchogram was attempted on the left. During the installation of the local anesthetic, the patient had a coughing spasm associated with shortness of breath and what was interpreted as acute dilation of the heart. This patient's illness apparently extended over a period of at least one year, and it was five months before the cardiac size returned to normal. Schwartz's case was characterized by multiple organ involvement including allergic rhinitis, bronchial asthma, anemia, purpura, arthralgia, polyneuritis, subcutaneous nodules, albuminuria, cardiac hypertrophy, and right bundle-branch block. The patient was ill for 18 months, and there was residual cardiac hypertrophy and right bundle-branch block. Schwartz presented his case as one of hyperergic disease with multiple system involvement which resembled Harkavy's syndrome.[4] This patient is being presented because of the association of eosinophilia and pulmonary infiltration with cardiac involvement and subsequent resolution.

Report of Case

History.—The patient was a 19-year-old white youth, graves registration clerk, who was admitted to Tokyo Army Hospital on March 16, 1955. He stated that five weeks prior to admission he worked out in the cold weather from 11 a.m. until evening. Subsequently he developed malaise, night sweats, and a cough productive of mucopurulent sputum which at times was blood-tinged. He was treated at his dispensary until March 2, 1955, at which time he was admitted to the local Army hospital. Two weeks after the onset of the present illness, he developed chest pain which was located more or less in the center of the chest and increased on breathing and coughing. The cough and chest pain improved. There was no history of pedal edema or palpitation. He was evacuated to Tokyo Army Hospital, arriving there March 16, 1955.

The patient lived in North Carolina prior to coming in the Army. When he was younger he worked in a tobacco plant, sweeping out the plant. He had no history of contact with fluorescent light bulbs or other dusts. He gave no history of exposure to tuberculosis. He was assigned to graves registration but had no direct contact with the remains.

Physical Examination.—The patient was a well-developed and thin white youth who was obviously short of breath. The blood pressure was 105/70. The pupils were equal and reacted to light and accommodation. Opthalmoscopic examination was normal. The throat and tongue were normal. The lungs were resonant with crepitant rales in the left base. Examination of the heart revealed the percussion dullness to be out to the anterior axillary line in the sixth intercostal space. The rhythm was regular, with no murmurs. Examination of the abdomen demonstrated tenderness in the right upper quadrant and dullness 1 to 2 cm. below the right costal margin. The liver, however, was not palpable. The genitalia and rectum were normal. There were a few small inguinal lymph nodes palpable. There was no other lymphadenopathy. There was no edema.

Laboratory Studies.—The complete blood cell count showed 13,050 white blood cells per cubic millimeter, with 45% neutrophiles, 13% lymphocytes, 1% monocytes, 41% eosinophiles. The hemoglobin was 11.3 gm. per 100 ml. The hematocrit was 34%. The blood urea nitrogen was 11.6 mg. per 100 ml. The urinalysis was normal. The A/G ratio was 3.5/2.9. The total protein was 6.4 gm. per 100 ml. The serum cholesterol was 121 mg. per 100 ml., with esters of 65. The alkaline phosphatase was 5 Bodansky units. The calcium was 11.1 mg. per 100 ml. Seven sputum examinations were negative for tubercle bacilli. Two sputum

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examinations were negative for parasites, larvae, and ova. A smear of the sputum showed 4% eosinophiles. One stool examination was positive for Strongyloides stercoralis larvae, and one was positive for hookworm ova. Subsequent stool examinations were negative for ova and parasites. The L. E. cell preparation was negative. The tuberculin test was slightly positive on the first strength and strongly positive on the second strength. The histoplasmin and coccidioidin tests were negative.

X-Ray Studies.—The chest x-ray taken on Feb. 28 at his dispensary (Fig. 1) showed a diffuse infiltration throughout the left lung and lower two-

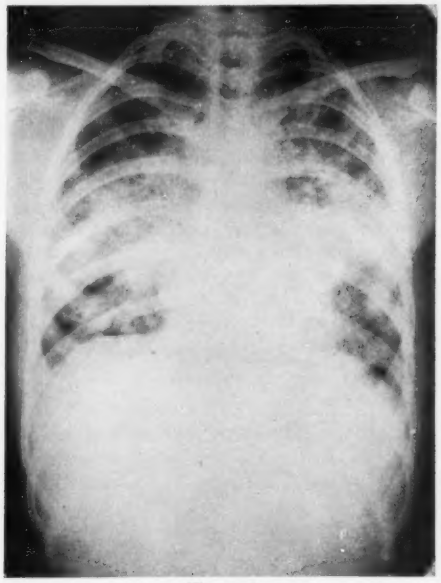

Figure 1

thirds of the right lung. The chest x-ray on March 17, 1955, (Fig 2) showed marked enlargement of the cardiac silhouette, with a diffuse granular infiltration throughout the left lung and the lower portion of the right lung. The chest x-ray of March 28, 1955, (Fig. 3) demonstrated clearing of the left lung. The pulmonary infiltration on the right was essentially unchanged, but there was now evidence of a pleural effusion on the right. There was increase in the transverse diameter of the heart since the previous examination. Chest x-ray of April 11, 1955, showed clearing of the bilateral pulmonary infiltration. There was almost complete disappearance of the right pleural effusion. The cardiac shadow was unchanged. The chest x-ray of April 18, 1955, showed clearing of the parenchymal infiltration, with decrease in the transverse diameter of the

Figure 2

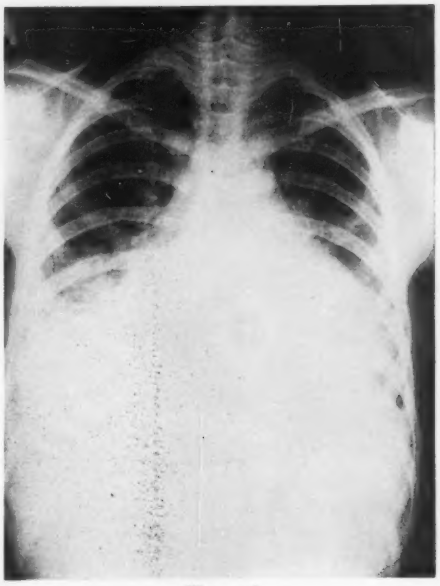

Figure 3

heart. The chest x-ray of May 2, 1955, showed increase in the infiltration in the right upper lobe, and a suggestion of an increased infiltration in the left upper lobe. The cardiac silhouette was still slightly enlarged. The chest x-ray of May 31, 1955, showed clearing of the pulmonary infiltra-

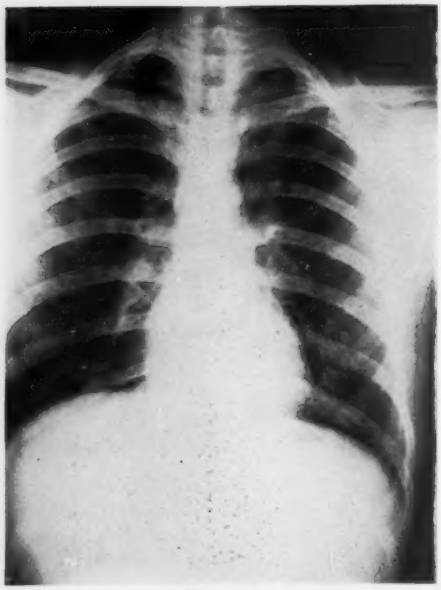

Figure 4

tions with increased lung markings. The cardiac shadow was within normal limits. Subsequent x-rays through July 13 showed progressive clearing of both lung fields. The x-ray of Aug. 1, 1955, (Fig. 4) was unchanged from July 13.

The cholecystogram, intravenous pyelogram, gastrointestinal series, and skeletal survey were negative.

Electrocardiograms.—The electrocardiogram of March 17, 1955, (Fig. 5) showed depressed ST segments in V_{2-6}. There were inverted T waves in Leads II, III, aV_F, V_{2-6}. The electrocardiogram of March 28, 1955, showed inverted T waves in Lead I, aV_L, and biphasic T waves in V_{2-6}. Subsequent electrocardiograms showed progressive improvement. By April 25, 1955, (Fig. 6), the electrocardiogram was within normal limits.

Hospital Course.—The patient was placed on bed rest. On admission, the temperature was 99.6 F. During the first four weeks of hospitalization he ran a low-grade fever, usually up to 100 to 101 F, with one spike to 103 F. Subsequently he was afebrile. The patient's clinical course was one of gradual improvement. The intestinal parasites were treated with hexylresorcinol and tetrachloroethylene. Since subsequent stool examinations

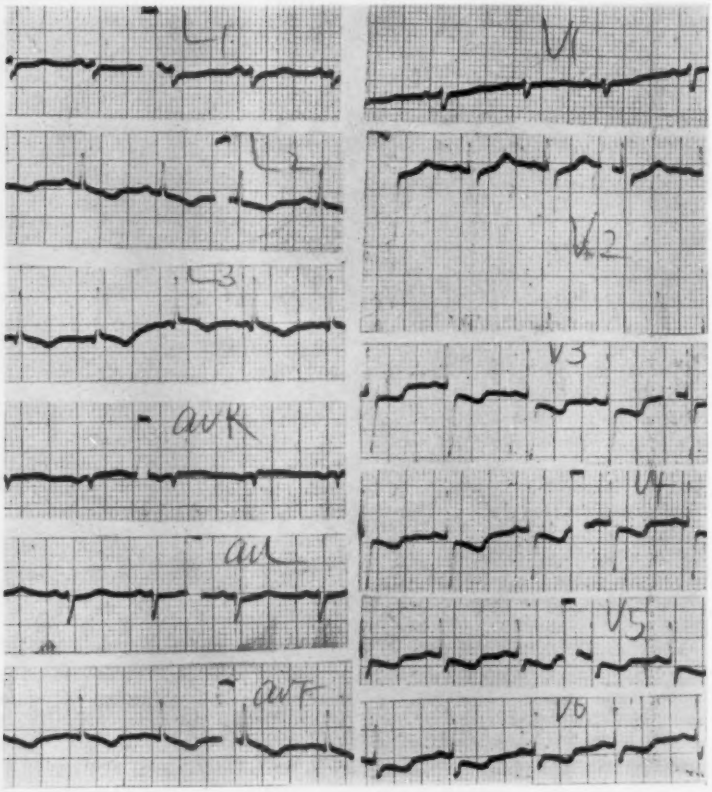

Figure 5

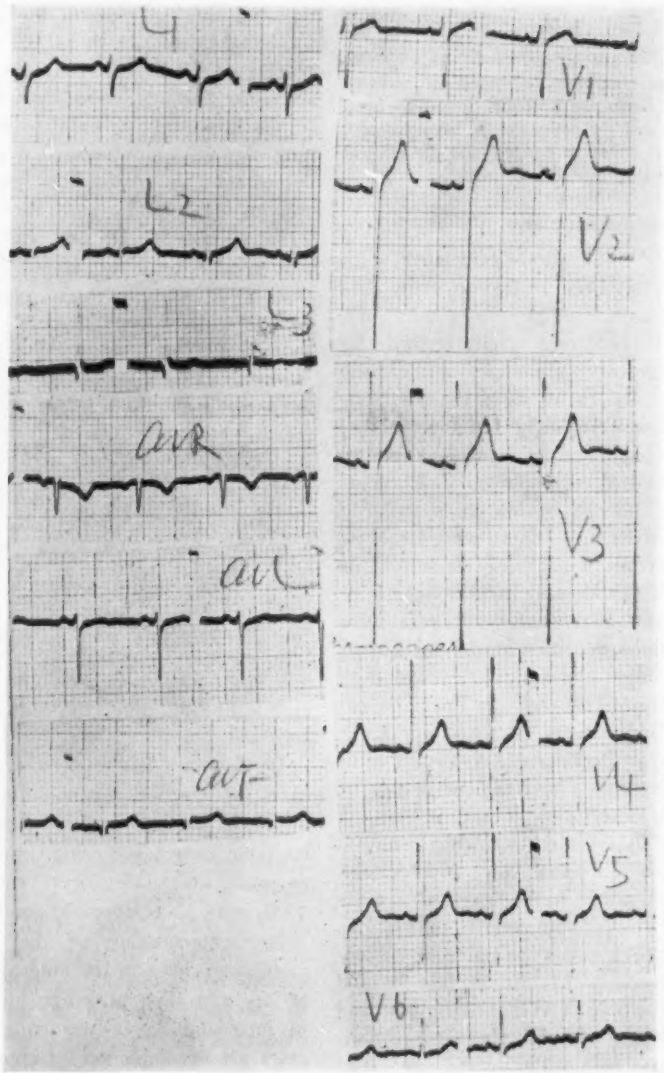

Figure 6

were negative, methylrosaniline chloride was not administered.

The x-rays described above show the main features of the hospital course. On April 9, 1955, a liver biopsy was done. The histological study showed the lobular architecture to be preserved. The liver cells were normal. There were many eosinophiles seen which were apparently in the sinusoids. The portal spaces were not abnormal. On April 15, 1955, a pericardial tap was attempted. Seven cubic centimeters of serosanguineous fluid was obtained. Culture of this fluid was negative for pyogens and tubercle bacilli. This patient had numerous complete blood cell counts. On April 8, 1955, the white blood cell count was 11,000 per cubic millimeter, with 44% eosinophiles and a hemoglobin of 11.3 gm. per 100 ml. On April 15 the white blood cell count was 11,000, with 52% eosinophiles and a hemoglobin of 12.4. The white blood cell count of May 6, 1955, was 8700, with 28% eosinophiles, and the hemoglobin was 12.4 gm. On June 3 the white blood cell count was 7650, with 11% eosinophiles and a hemoglobin of 14.9. The white blood cell count of July 30, 1955,

showed 6950, with 9% eosinophiles, 60% neutrophiles, 29% lymphocytes, 2% monocytes. The hemoglobin was 15.1 gm. per 100 ml. By Aug. 9, 1955, the patient was completely ambulated and ready to be discharged from the hospital. Follow-up Sept. 12, 1955, revealed the patient to be asymptomatic. The chest x-ray was unchanged, and the electrocardiogram was within normal limits.

Comment

Pulmonary infiltration associated with eosinophilia has been related to many different causes. Loeffler [5] originally described the syndrome characterized by fleeting, migratory pulmonary infiltrations and eosinophilia. In his cases the outstanding symptoms were slight fatigue, malaise, productive cough, and mucopurulent sputum which contained eosinophiles. The roentgenographic picture in his cases took on many different forms. There were large, irregular opacities which were unilateral or bilateral. Others showed infraclavicular infiltrations and hilar shadows. There were sharply defined densities at the margin of the lobes. Single and multiple circular densities sometimes occurred. In Loeffler's patients, the infiltrations persisted for three to eight days. Occasionally a pleural effusion was present. The transient nature of this original description is quite in contrast to some of Mark's cases,[2] which showed quite extensive pulmonary involvement. Vines and Clark [18] have described a quite protracted case of pulmonary infiltrations and eosinophilia under the name of eosinophilic pneumonopathy, which was treated with corticotropin (ACTH). Bayley and associates [6] have reported the autopsy findings in a case of Loeffler's syndrome. The outstanding features were large numbers of eosinophiles in the pneumonic exudate. There was organization of the exudate characterized by fibrosis and giant cells. There were also granulomatous lesions and necrotizing arteritis and phlebitis. The granulomatous nodules were characterized by fibrinoid swelling and necrosis of collagen. There were large numbers of eosinophiles in the peripheral portion of the lesion. Meyenburg, cited by Alpher, [7] has reported the pathological finding of four accidental deaths which he felt fulfilled the criteria of Loeffler's syndrome. The characteristic findings were hyperemia and a serofibrinous cellular exudate involving the lung alveoli, which showed a predominant percentage of eosinophiles, with accompanying eosinophilic infiltration of the interstitial tissues. In one case, increased eosinophiles were found in the liver. In two, there were increased eosinophiles in the spleen and bone marrow. My patient showed increased eosinophiles in the liver.

Velzeboer [8] has described a case of Loeffler's syndrome with ocular manifestations which were characterized by infiltration of the retina with residual areas of scarring. Jones and Ogle [9] have reported skin manifestations in Loeffler's syndrome characterized by irregularly shaped, erythematous, macular lesions of the face, neck, trunk, and dorsum of the feet, with those on the lower abdomen having a bluish tinge. On the second day, dull red areas of variable size appeared in the pubic area. By the eighth hospital day, the skin lesions had subsided.

De Zoyosa [10] has reported a series of 912 cases of tropical eosinophilia. This syndrome is characterized by a persistent, intractable cough, wheezing, mucoid sputum, dyspnea, and a leucocyte count of over 4000, with an eosinophile count over 20%. The roentgenogram of the chest shows mottled shadows in the lungs. It may begin at any age. The peak age incidence is 27 in men and 35 in women. Most of the cases are accompanied by upper substernal pain. Fifteen per cent of de Zoyosa's patients did not progress beyond the stage of cough. These represent the abortive type. Acute types were rare in his series and took the form of pleuritis, pneumonia, pseudotuberculosis, hemoptysis, angina-like symptoms, dysentery, and prolonged fever. Some were characterized by chronic asthma. In children, he described three clinical types: the recurrent bronchitis type, the coryzal type, and the bronchopneumonic

type. The x-ray picture in adults is quite varied in tropical eosinophilia. The commonest picture was a ground-glass appearance in the involved lung. However, other cases may show miliary mottling, vascular accentuation, pleural effusion, bronchopneumonic and pneumonic consolidation, peribronchial fibrosis, or vascular nodulation. Two outstanding features of this disease are occurrence only in the tropics and response to arsenical treatment.

Harkavy * has reported a series of 16 cases of bronchial asthma which present unusual clinical manifestations. In this series, asthmatic symptoms, disease of the sinuses, temperatures 99 to 104 F, recurrent pulmonary infiltrations, pleural effusions, myocardial disease, mild anemia, leucocytosis, and eosinophilia may occur. The cases were characterized by hyperergic responses limited to two or three organs, such as the sinuses, heart, and lungs. Some of his cases led to a fatal termination with hyperergic and anergic involvement principally of the lungs, myocardium, and serous membranes. Two of his cases showed periarteritis nodosa.

It would seem that all of these cases of pulmonary infiltration with eosinophilia represent an allergic response, with the lungs as the shock organ. The relationship of parasitic infestation, particularly amebiasis, ascariasis, trichinosis, filariasis, human hookworm, and creeping eruption [12] has been repeatedly suggested. Ascaris, hookworm, and Strongyloides have the lungs as a necessary part of their life cycle. My patient had Strongyloides and hookworm infestation. Pulmonary infiltrations with eosinophilia have been associated with ragweed pollen,[7] privet pollen,[5] aminosalicylic acid administration,[13] and vaginal cream [14] containing a sulfonamide. Radke's [15] case is attributed to bronchiectasis. Harkavy [11] felt that the chief precipitating factor in his patients was bacterial allergy with chronic sinusitis. In 7 of his 16 cases, pollen and food hypersensitization were considered to have additional exciting roles.

The case in this presentation was manifested by diffuse pulmonary infiltrations, cardiac involvement, anemia, eosinophilia, and increased eosinophiles in the liver sinusoids, with gradual but definite recovery in a period of five months without therapy. Because of this progressive improvement, corticotropin was not administered, as has been suggested by Herbert and associates.[16] The patient presented in this report would seem to fit into the general class of Loeffler's syndrome. The exact cause of the cardiac involvement is not certain. It may have been partly related to the intrapulmonary disease with resulting cor pulmonale. However, there were no peripheral signs of right heart failure, and the electrocardiogram did not show right ventricular hypertrophy. There may have been participation of the myocardium and pericardium in the general allergic response. An attempted pericardial tap yielded only 7 cu. cm. of fluid. The cardiac involvement in this case resembles Harkavy's † patients; however, one of Mark's [2] cases described above presented cardiac involvement. Hoffman and Schwartz [17] have reported a case of pulmonary infiltration with eosinophilia with a protracted course which they felt resembled both Loeffler's syndrome and tropical eosinophilia. It would seem that the best explanation of the etiology of these cases, because of the widespread manifestations, would be a hyperergic response of the vascular system to some allergen. This would explain the involvement of the lungs, eyes, hematopoietic system, liver, heart, and skin.

Summary

A case of Loeffler's syndrome associated with cardiac involvement is reported. The pertinent literature of pulmonary infiltrations associated with eosinophilia is reviewed. It is postulated that these cases may be explained as a hyperergic response of the vascular system to some allergen. This would explain the widespread involvement

* References 4 and 11.

† References 4 and 11.

in some cases of lungs, eyes, hematopoietic system, liver, heart, and skin.

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THE SYNDROME OF PSEUDO-PSEUDOHYPOPARATHYROIDISM

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ALBRIGHT and associates,[1] in 1942, described a group of patients with hypocalcemia, hyperphosphatemia, ectopic calcification and ossification, dyschondroplasia manifested by short metacarpal and metatarsal bones, and a characteristic short, round body and round face. Tetany, convulsive symptoms, lenticular opacities, and calcification of the basal ganglia were also present. Unlike persons with idiopathic hypoparathyroidism, these patients had normal parathyroid glands and there was little or no phosphate diuresis in response to the administration of parathyroid extract. Having named this syndrome pseudohypoparathyroidism, Albright and associates * postulated the presence of multiple, independent genetic defects to account for the stigmata noted and suggested that the hypocalcemia and hyperphosphatemia resulted from a failure of end-organ response to endogenous parathyroid hormone.

Subsequently, there appeared case reports [3] of persons with some but not all of the stigmata described by Albright and associates. The term pseudo-pseudohypoparathyroidism has been applied to the condition in which hypocalcemia (and resultant tetany and convulsive symptoms) and hyperphosphatemia are absent but ectopic ossification, dyschondroplasia, and short stature and round face are present. Peculiarly, calcification of the basal ganglia has not been noted in this group despite the presence of ectopic calcification and ossification in other body areas.

The present report concerns a patient with many characteristics of pseudo-pseudohypoparathyroidism and an unusual type of dyschondroplasia. He also has gout, unexplained splenomegaly and lymphoid hyperplasia, and asymptomatic rheumatoid spondylitis.

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* References 1 and 2.

Report of Case

In August, 1954, a 24-year-old white man, a machinist, developed mild aching in the right ankle two days after an inguinal herniorraphy. This progressed to severe inflammation, and several days later similar changes appeared in the right knee. Treatment by joint aspiration and with salicylates did not produce immediate relief, but the process gradually subsided after several days' rest. No further symptoms were noted until March, 1955, when inflammation of the metatarsophalangeal joint of the left hallux, left ankle, and left knee developed, resulting in admission to the Salt Lake Veterans Administration Hospital. The patient attributed the recurrence of this process to the trauma of ill-fitting shoes. Fever, chills, and preceding infections were denied.

Review of symptoms and past history were unremarkable except for the presence of very short thumbs since birth. Two siblings, the patient's parents, and all other known relatives were free of recognized deformities. His mother and father were 63 in. and 69 in. tall, respectively. A 23-year-old sister measured 65 in. and was obese. A 17-year-old brother was 69 in. tall. Only the patient's sister could be considered to be round-faced. The hands of all members of the immediate family were normal except for the father, whose thumbs appeared short. A maternal uncle had gout.

Physical examination revealed a short, stocky, young white man of average intelligence (Fig. 1). His height was 65½ in. The temperature was 99 F, respirations 16 per minute, pulse 88 per minute, and the blood pressure 135/95. The blood pressure dropped to 115/70 after two days of hospitalization and remained in the normal range thereafter. The skin, head and neck, chest, and heart were unremarkable except for small, shotty cervical nodes. Obvious splenomegaly was present, and a ptotic liver of normal size was palpable. Examination

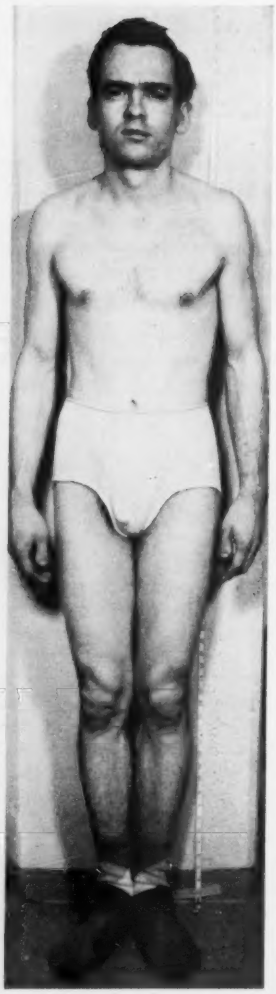

Fig. 1.—Photograph of patient, 24-year-old white man. Height 65½ in.

of the genitalia and rectum was normal. There was bilateral, shotty, nontender, epicondylar, axillary, and inguinal lymphadenopathy. The left knee, ankle, and hallux showed moderate diffuse swelling, erythema, and tenderness to palpation. A violaceous discoloration of the skin covered the dorsum of the left foot. Point tenderness was exquisite on the plantar aspect of the metatarsophalangeal joint of the left hallux. The fingers were generally short and stubby. The thumbs were markedly short (Fig. 2). Neurological examination was unremarkable.

Initial laboratory studies revealed a volume of packed red cells of 44% and white blood cell count of 7600 per cubic millimeter, with 78% neutrophiles, 14% lymphocytes, 7% monocytes, and 1% eosinophiles. The red blood cells were normochromic and normocytic on smear, and the platelets appeared adequate in number and configuration. Urinalysis revealed 1+ albuminuria, no formed elements in the sediment, and no other abnormalities. Initial determinations of the blood urea nitrogen ranged from 25 to 35 mg. per 100 ml. The serum creatinine was 2.1 mg. per 100 ml., and the serum uric acid, 10.2 mg. per 100 ml. The phenolsulfonphthalein excretion was 15% of the injected dose in 15 minutes and 42% of the injected dose in 2 hours. The endogenous creatinine clearance was 50 ml. per minute.

The following tests gave results in the normal range: total protein and A/G ratio, blood sugar, serum electrolytes, serum cholesterol, serum calcium, serum phosphorus, serum alkaline phosphatase, serum bilirubin, serum thymol turbidity, serum sulfobromophthalein (Bromsulphthalein) retention, VDRL serologic test for syphilis, stool guaiac, antistreptolysin titer, lupus erythematosus cell preparation, and Brucella agglutinin titer. An ECG was normal. Joint fluid (left knee) was viscid and of a turbid yellow color. The total protein was 5.3 gm. per 100 ml., and the leucocyte count 3500 per cubic millimeter. One hundred per cent of the leucocytes were neutrophiles. The fluid clotted upon standing.

Fig. 2.—Photograph of patient's hands. Note generally stubby fingers and exceptionally short thumbs.

Chest x-rays were normal. An intravenous pyelogram showed good concentration of dye, well-visualized kidney shadows of normal size, and normal calyceal systems. X-rays of the skull, arms, legs, hands, and feet revealed numerous small calcific densities in the soft tissues, about joints, and along muscle sheaths (Fig. 3, 4, and 5). Some of these were amorphous in appearance; others showed osseous trabeculation. There was no intracranial calcification. The distal phalanges of the thumbs and middle fingers were abnormally short, but all the metacarpal and metatarsal bones were of normal length (Figs. 3 and 4). Lumbosacral films showed changes in the density and in the trabeculation of the bone adjacent to the sacroiliac joints, suggestive of rheumatoid spondylitis. A lymph-node biopsy showed fibrosis and nonspecific hyperplasia. A liver biopsy was normal. Skin and subcutaneous tissue biopsy revealed normal skin overlying soft tissue calcification and ossification. An attempted splenic aspiration was unsuccessful.

Fig. 3.—Roentgenogram of patient's hands. Metacarpal bones are of normal length. First and third distal phalanges are abnormally short. Note multiple small calcific densities in soft tissues.

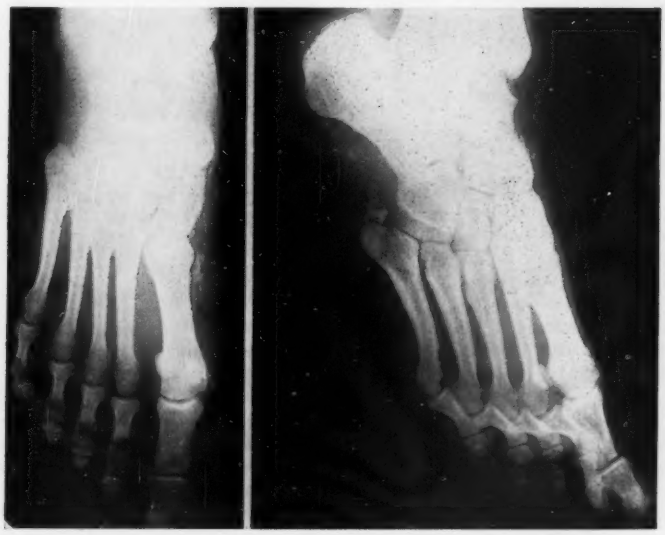

Fig. 4.—Roentgenograms of patient's right foot. Metatarsal bones are of normal length. Multiple calcific densities are present in soft tissues.

Fig. 5.—Roentgenogram of patient's skull. Multiple calcific densities are present in the scalp tissues. There is no intracranial calcification.

The patient was hospitalized for nine weeks and was afebrile except for a three-day exacerbation of arthritis during the fourth week. Initial treatment with salicylates and alkalinizing salts resulted in very gradual improvement in the arthritis. The blood urea nitrogen and serum uric acid concentrations decreased to 15 mg. and 6.5 mg. per 100 ml., respectively. Improvement in the endogenous creatinine clearance and urinary phenolsulfonphthalein excretion was also noted. No treatment was given during the second and third hospital weeks. In the fourth week, probenecid therapy was instituted. The blood urea nitrogen concentration subsequently rose to 45 mg. per 100 ml., and deterioration of other renal function tests ensued. The deposition of uric acid sludge in renal parenchyma was believed responsible for this, since improvement in renal function followed alkalinization of the urine. An exacerbation of arthritis, which required colchicine for control, followed a splenic aspiration in the fourth week of hospitalization.

Satisfactory therapeutic results were achieved by the ninth hospital week, and on discharge the blood urea nitrogen concentration was 10 mg. per 100 ml. and the serum uric acid concentration 6.2 mg. per 100 ml. The patient was advised to follow a regimen of a low purine, 50 gm. protein diet, probenecid, 1.5 gm. daily, sodium bicarbonate, 8 gm. daily, and colchicine, 1 mg. each morning. The splenomegaly and lymphadenopathy were unchanged at the time of discharge.

The patient was readmitted in October, 1955, for reevaluation. He had remained well and had continued taking probenecid and colchicine in the prescribed doses but had discontinued the sodium bicarbonate. Physical examination was unchanged except for the absence of arthritis. A complete blood cell count and urinalysis were normal. The blood urea nitrogen concentration was 17 mg. per 100 ml., and the serum creatinine concentration, 1.9 mg. per 100 ml. The serum calcium and serum phosphorus concentrations were 9.8 mg. and 3.2 mg. per 100 ml., respectively. Serum uric acid and serum alkaline phosphatase determinations were not obtained. An Ellsworth-Howard test[4] resulted in a twofold increase in urine phosphorus excretion in response to the administration of 200 units of parathyroid extract (Eli Lilly & Company) intravenously (Fig. 6). This represents a response in the low normal range. A normal patient showed a fourfold increase when given an injection of a similar dose of parathyroid extract of the same lot number. The intravenous administration of calcium resulted in a normal decrease in urinary excretion of phosphate, an effect believed to require intact parathyroid function.[5]

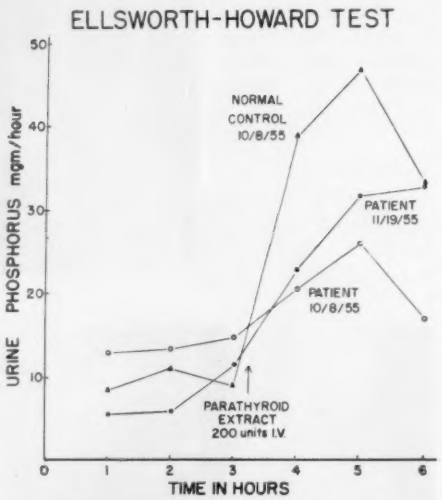

Fig. 6.—Ellsworth-Howard tests in patient and a normal control. Study on Oct. 8, 1955, was during probenecid therapy, while study of Nov. 19, 1955, was performed one month after probenecid had been discontinued.

Probenecid was discontinued for one month and

a second Ellsworth-Howard test performed. This test resulted in a slightly greater phosphorus diuresis than previously (Fig. 6). No significant change in the serum phosphorus level could be demonstrated between the two test periods, but the endogenous creatinine clearance had increased from 51 ml/min. to 65 ml/min. in the interval. After the second test the patient resumed probenecid and sodium bicarbonate therapy and has remained well to the present time despite a persistently elevated serum uric acid level and despite an adequately increased uric acid excretion in response to probenecid. In February, 1956, the blood urea nitrogen and serum uric acid concentrations were 9 mg. and 7.9 mg. per 100 ml., respectively. Serum creatinine concentration was 2.4 mg. per 100 ml., and the endogenous creatinine clearance was 43 ml/minute. A phenolsulfonphthalein excretion test resulted in excretion of 22% of the injected dose in 15 minutes and 68% of the injected dose in 2 hours. The 24-hour urine uric acid excretion was 860 mg. per 24 hours.

In August, 1956, the serum uric acid level and a renal biopsy were normal.

Comment

Three patients with pseudo-pseudohypoparathyroidism have been reported in the world literature.† Albright's patient [3] was a 29-year-old woman with the typical habitus, facial contour, dyschondroplastic changes, and ectopic calcification and ossification of pseudohypoparathyroidism, but with normal serum calcium and phosphorus concentrations. This patient had severe hypertension and a past history of an ill-defined, acute illness with albuminuria. At the time of study, there was no gross evidence of renal disease, and phenolsulfonphthalein excretion was "excellent." Other tests of renal function were not reported. A renal biopsy taken during thoracolumbar sympathectomy revealed a peculiar dilatation of Henle's loops as well as the characteristic changes of nephrosclerosis. Neither the patient nor a normal control subject showed a phosphate diuresis following the administration of parathyroid extract, whereas a hypoparathyroid patient "showed a moderate response." An extract of low potency was believed responsible for this.

In 1955, two more patients were described. The patient of Miles and Elrick [6] was a 25-year-old woman with all the typical stigmata, except for ectopic calcification or ossification. A normal serum calcium concentration and an adequate response to parathyroid extract were demonstrated. Roche's patient, a 40-year-old man,[7] had mild dyschondroplasia, ectopic ossification limited to exostoses at the sites of muscle attachment, and rather normal body configuration and facial contour. His serum calcium and phosphorus concentrations were normal, there was no overt renal disease, and his response to parathyroid extract was in the low range of normal. The potency of this extract was not tested in a normal person. Table 1 represents an arbitrary 0 to 4+ grading of the reported cases with respect to the expected features of this syndrome.

Excluding the equivocal response to parathyroid extract, Albright's patient represents the prototype of the syndrome. The remaining patients show certain variations. In the patient reported here, subcutaneous ossification is striking, but short metacarpal and metatarsal bones and markedly short stature and round face are not present. Restriction of the dyschondroplasia to short distal phalanges is most interesting, since this is usually a minor feature of pseudo-pseudohypoparathyroidism but often a major dyschondroplastic defect in myositis ossificans progressiva.‡

It is difficult to relate gout to pseudo-pseudohypoparathyroidism. The hereditary nature of gout is well established, but the role of heredity in idiopathic hypoparathyroidism, pseudohypoparathyroidism, and pseudo-pseudohypoparathyroidism is unclear. Steinberg and Waldron [8] found one report of idiopathic hypoparathyroidism in siblings in over

† References 3, 6, and 7.

‡ References 12 and 13.

TABLE 1.—*Comparison of Reported Cases of Pseudo-Pseudohypoparathyroidism on the Basis of Expected Findings, Arbitrarily Graded Zero to Four Plus*

Patient	Response to Parathyroid Hormone	Normal Serum Calcium and Phosphorus	Ectopic Ossification	Lenticular Opacities	Basal Ganglia Calcification	Dyschondroplasia	Short Stature, Round Face
Albright and coworkers	?	++++	++++	0	0	++++	++++
Miles and Elrick	++++	++++	0	++	0	++++	++++
Roche	++	++++	++	++++	0	++	+
Wallach, Englert, and Brown	+++	++++	++++	0	0	++	+

50 cases. However, a review of over 35 cases of pseudohypoparathyroidism in the world literature reveals five instances of familial incidence. § One of these involved a parent and child.[16] No familial incidence has been reported in the four known cases of pseudo-pseudohypoparathyroidism. Physical and roentgen examination of the present patient's immediate family failed to reveal any of the stigmata of these diseases.

Albright has concluded that pseudohypoparathyroidism and pseudo-pseudohypoparathyroidism are the result of gene-determined defects. He called attention to certain similarities of these two syndromes and myositis ossificans progressiva but did not include idiopathic hypoparathyroidism among this group of disorders. Certain modifications of this view appear to be warranted.

The failure to demonstrate clear-cut hereditary transmission of the stigmata of these disorders suggests the possibility that they are the result of errors in fetal development resulting from injury in utero. Recent studies[19] have shown that fetal development and organ differentiation are orderly processes occurring with a degree of temporal regularity and predictability. Certain types of fetal damage can regularly be produced by imposing unfavorable conditions, such as anoxia, during specified times. Many organs and systems may be at a crucial point in development at any one time, and multiple defects in unrelated organ systems are to be expected. Such an occurrence appears to be the most plausible explanation for certain congenital syndromes, such as Turner's syndrome and Marfan's syndrome.

A number of organs involved in the syndromes under discussion are in a crucial state of development during the sixth, seventh, and eighth weeks of fetal life. The parathyroid anlagen separate from their parent pharyngeal pouches and move caudad in the seventh week. Cellular differentiation of the glands occurs in the eighth week. At about the same time, the cartilaginous model of the appendicular skeleton has completed a period of development with concentration of mesenchyme and formation of detectable primordia of the small bones of the hands and feet. The lens placode of the eye develops in the fifth week, and in the sixth week, elongation of cells on the deep pole occurs, presaging transformation into lens fibers.[18] Thus, fetal injury occurring at about the seventh week of development could result in the disorders under discussion. If such is the case, repetition of such injury as a result of defective uterine environment in successive pregnancies can account for the appearance of these syndromes in siblings. The degree of injury determines the stigmata noted, and the disorders under discussion are thus a group of syndromes within a single spectrum. Six developmental anomalies capable of

§ References 2 and 15-17.

qualitative and quantitative variation are postulated (Table 2).

TABLE 2.—*Comparison of Various Syndromes on the Basis of Stigmata: Postulated Developmental Anomalies*

Syndrome	Parathyroid Deficiency (1)	Parathormone Unresponsiveness (2)	Lenticular Opacities (3)	Ectopic Calcification and Ossification (4)	Dyschondroplasia (5)	Short Stature and Round Face (6)
Idiopathic hypoparathyroidism	+	0	+	+	0	0
Pseudohypoparathyroidism	0	+	+	+	+	+
Pseudo-pseudohypoparathyroidism	0	0	+	+*	+	+
Myositis ossificans progressiva	0	0	0	+*	+	0

* Basal ganglia calcification not seen in pseudo-pseudohypoparathyroidism or myositis ossificans progressiva

Idiopathic hypoparathyroidism is included in this spectrum because of certain evidence that most cases are developmental in origin. Steinberg and Waldron have shown that the large majority of cases have their onset in the first and second decades of life. Of three autopsied cases, || the parathyroid glands were completely absent in two.¶ Most importantly, idiopathic hypoparathyroidism is often associated with lenticular opacities and ectopic calcification, two phenomena seen in pseudo-pseudohypoparathyroidism in the absence of hypocalcemia or deficient parathyroid function and in the presence of other obviously developmental defects. Such characteristics would be most unusual for an acquired disease.

The present case report suggests the advisability of including myositis ossificans progressiva # in this spectrum of diseases. This rare and peculiar entity is characterized by massive, crippling ectopic ossification throughout the body musculature in association with dyschondroplastic changes in the digits. Rosenstirn's case [12] showed not only short distal phalanges and anomalies of the bones of the halluces but also short fourth metatarsals. In other cases reviewed by the same author, short metacarpal and metatarsal bones were likewise present. In contrast, Reynold's patient [14] with pseudohypoparathyroidism exhibited the expected hypocalcemia, lack of response to parathyroid extract, ectopic calcification, and short first metacarpal bones, but also had short distal phalanges. The patient in the present report shows characteristics intermediate between these two examples.

At the present time, it is impossible to predict a relationship among the various major defects of the spectrum. No single factor capable of producing the observed stigmata is known. The explanation may lie in the fact that all the organs and systems involved are undergoing crucial development at the time a noxious influence is imposed.

Summary

The fourth reported case of the syndrome of pseudo-pseudohypoparathyroidism is presented, and certain variations from the classical picture are discussed. It is suggested that idiopathic hypoparathyroidism, pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism, and myositis ossificans progressiva result from a series of related developmental anomalies which may vary both

|| References 8-11.

¶ References 8-10.

References 12 and 13.

qualitatively and quantitatively to produce a spectrum of related syndromes.

Dr. O. N. Rambo Jr., Dr. J. J. Wolfson, and Dr. D. W. Stowell provided the pathologic and roentgenographic descriptions, and Mr. E. L. Simons and Mr. G. Tanner gave technical assistance.

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HEPATITIS COMPLICATING MUMPS

MAJOR WILLARD R. WARREN (MC), U. S. Army

OF THE commonly encountered acute infectious diseases, perhaps none is more protean in its manifestations and potentialities than mumps. Although usually this disease is clinically a benign infection confined to the salivary glands, it may on occasion attack the gonads, pancreas, nervous system, mammary glands, heart, labyrinth, eyes, kidneys, prostrate, thyroid, thymus, or intestinal glands,* singly or in combination, sometimes in the absence of demonstrable parotid involvement. The invasive possibilities of this versatile virus would seem to be almost limitless, and it has been appropriately termed a pantropic agent.

Recently a patient was observed who developed an acute hepatitis, ostensibly due to the mumps virus, in the course of a typical attack of mumps, and in view of the rarity of this complication the case will be reported in detail.

Report of a Case

The patient, a 35-year-old white officer, was admitted to the Communicable Disease Section of the 320th General Hospital on Feb. 2, 1954, with the chief complaint of swelling of the left testis of one day's duration. He had been well until the day before admission, when his left testis became swollen, painful, and tender. The next day he developed feverishness, epigastric pain, and swelling of the right parotid and was admitted to the hospital with a diagnosis of mumps.

Past History.—Past history was not remarkable aside from an episode of jaundice in 1943, diagnosed as infectious hepatitis and treated with a high-carbohydrate diet and 10 days of bed rest in a dispensary. Following his return to duty he remained well and had never had a recurrence of jaundice or gastrointestinal symptoms referable to hepatic disease. He denied excessive use of alcohol or exposure to hepatotoxic agents.

Physical Examination.—Physical examination revealed a well-developed, slightly obese, middle-aged white man who appeared acutely ill and uncomfortable. Rectal temperature was 101 F. There was moderate swelling of the right parotid gland; other salivary glands were normal. The orifice of the right Stenson's duct was inflamed. The liver edge was palpable 2 or 3 cm. below the right costal margin, and the organ was moderately tender. The spleen was not enlarged. There was moderate swelling and marked tenderness of the left testis and mild swelling and tenderness of the right epididymis. No other abnormal physical findings were noted.

Laboratory Examinations.—Laboratory examinations at admission disclosed normal blood cell count, urinalysis, and roentgenogram of the chest. Thymol turbidity was 7.1 Maclagan units. Serum amylase was 139 units (the upper limit of normal for this laboratory being 135 units); subsequent serum amylase levels were 175 units on Feb. 10 and 160 units on Feb. 20.

Hospital Course.—Upon admission a diagnosis of acute parotitis, orchitis, and epididymitis due to mumps was made, and the patient was placed on a regimen consisting of bed rest with bathroom privileges, warm alkaline aromatic solution mouth washes, 2 mg. of diethylstilbestrol three times daily, and analgesics as indicated for control of discomfort. On this program his progress appeared to be satisfactory until Feb. 5, when yellow sclerae and dark urine were noted by the ward nurse. At about this time the patient commenced to complain of severe anorexia and occasional nausea, which persisted for several weeks thereafter. Physical examination on Feb. 6 confirmed the presence of definite mild scleral icterus; the liver was now enlarged to 4 or 5 cm. below the right costal margin and markedly tender. Owing to the intervention of a week-end, it was impossible to obtain liver function tests until Feb. 8; the results (Table) supported the clinical impression of acute hepatitis, though by then the mild icterus had faded and the total serum bilirubin was normal.

The hepatic complication was managed with continued bed rest and moderate doses of dried yeast, and dimenhydrinate (Dramamine) was ad-

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* References 1 and 2.

Results of Liver Function Tests

	Feb. 8	Feb. 10	Feb. 16	Feb. 23	March 2
Sulfobromophthalein (% retention 45 min.)	----	----	13.2	2.8	3.4
Cephalin flocculation (24 hr.)	2+	----	2+	Neg.	2+
Thymol turbidity (Maclagan units)	15.2	----	11.4	12.3	9.6
Total serum bilirubin (mg. per 100 ml.)	0.96	0.59	0.43	0.23	0.38
1 min. serum bilirubin (mg. per 100 ml.)	0.32	0.21	0.13	0.10	0.13
Alkaline phosphatase (Bodansky units)	6.4	----	----	2.4	----

ministered as necessary to combat nausea. The patient ran an irregular fever with temperature up to 102.2 F from admission until Feb. 8, when his temperature became normal and remained so. His parotitis and orchitis improved progressively; by Feb. 18 both had cleared completely, and diethylstilbestrol therapy was terminated. He continued to have intermittant anorexia, however, and his liver remained moderately enlarged and tender until the latter part of February, when symptomatic improvement first became evident and the liver began to diminish in size. By the first week in March he was asymptomatic, and the liver was normal in size and only slightly tender. Serial liver function tests (Table) showed varying degrees of abnormality but a general tendency toward improvement; by March 2 the sulfobromophthalein (Bromsulphalein) and one-minute serum bilirubin had returned to normal, though the thymol turbidity remained elevated. He was mobilized progressively in the first week in March without ill effects, and was discharged to duty on March 9. Follow-up subsequent to discharge revealed that he remained asymptomatic and had no further evidence of residual hepatic disease.

Comment

The diagnosis of acute hepatitis in this patient would seem to be well substantiated by the presence of clinical icterus, unequivocal hepatomegaly, hepatic tenderness, and subsequently elevation of the one-minute serum bilirubin (0.32 mg. per 100 ml.) and abnormal retention of sulfobromophthalein (13.2% at the end of 45 minutes). The elevated values in the thymol turbidity and serum aklaline prosphatase tests are also compatible with a diagnosis of hepatic parenchymal disease, though their significance in this instance is diminished by the fact that the thymol turbidity is frequently, and the alkaline phosphatase rarely, elevated in patients with mumps who have no manifest hepatic involvement.[3]

The possibility that the patient's jaundice was due to other causes, such as obstruction of the biliary tract, should perhaps be considered. Mumps is occasionally complicated by an acute pancreatitis, and conceivably pressure arising from an acutely inflamed and edematous pancreas could cause some degree of obstruction of the common bile duct. This patient had, however, no symptoms or physical signs to support a diagnosis of acute pancreatitis, and the hyperamylasemia which he displayed is a common feature of mumps in the absence of pancreatic involvement.[2] Neither was there any reason to suspect other possible causes of biliary obstruction nor a fortuitous occurrence of other unrelated icterogenic diseases, such as cirrhosis, hemolytic anemia, or liver damage due to exposure to hepatoxic agents. Diethylstilbestrol, of which the patient received 6 mg. daily during his first 16 days in the hospital and which may have contributed to his symptoms of nausea and anorexia, is not known to produce hepatic injury.[4]

Since the patient had been resident for several months in Germany, a country where viral hepatitis is strongly endemic, it might be argued that his liver disease represented simply an attack of acute infectious hepatitis which manifested itself coincidentally at the same time as his mumps. Against this thesis are the facts that he had had no recent contacts with jaundiced persons and that hepatitis was not particularly prevalent in the surrounding military population at the time. Moreover, the patient had had a previous attack of infectious hepatitis, which generally confers a life-long immunity, and even with no past history of the disease susceptibility to the usual form of viral hepatitis is relatively low after the age of 30.[5] Thus,

although an intercurrent attack of acute infectious hepatitis cannot be excluded, it would seem an implausible explanation of the hepatic phenomena which this patient exhibited.

On the basis of the foregoing considerations it appears reasonable to assume that this patient did have an acute hepatitis complicating a relatively severe mumps infection and that the etiologic agent responsible for this hepatitis was in all probability the mumps virus.

Hepatitis is evidently an exceedingly rare manifestation of mumps. Although Pullen [6] lists hepatitis among the occasional complications of this illness, other standard textbooks of communicable disease or virology† make no mention of it. Moreover, a recent survey of the medical literature available to the Armed Forces Medical Library disclosed only two reports referring to the occurrence of jaundice or hepatitis in the course of mumps. Browne,[9] describing a severe case of mumps complicated by orchitis and pancreatitis, noted yellow sclerae among the physical findings when the patient was first examined, five days after the onset of salivary adenitis. No further details were provided regarding the status of the liver or the subsequent course of jaundice. McNicholl [10] observed two cases of jaundice complicating mumps, one in a boy of 4 years and another in an adult, the icterus appearing respectively one week and five weeks after the onset of the parotitis. Each of these patients had "considerable" jaundice and hepatic enlargement, the duration of which was not specified. Unfortunately, detailed studies could not be carried out. The author stated that he could find no reference to this complication in the medical literature. Both of the above reports were very brief communications which suggest but by no means establish that mumps hepatitis exists as a definite entity.

Because of the interest engendered by the patient herein reported, a series of 44 cases of mumps was studied carefully for clinical evidence of hepatic disease, and on 26 of these various liver function tests were performed.[3] No other instance of icterus, hepatomegaly, or definite biochemical evidence of hepatic damage was detected. Although the thymol turbidity test showed elevated values in over half of these patients, in the absence of other convincing indications of hepatic dysfunction it was concluded that these results were probably due to alterations in γ-globulin attendant upon an acute infectious disease.[11]

To evaluate further the validity and significance of hepatitis complicating mumps, it would seem profitable to perform liver function tests on a much larger series of mumps patients and to carry out detailed studies, including liver biopsy, on any cases of jaundice or hepatomegaly which might be encountered. Because of the potential seriousness of any form of liver damage, a definite answer to the riddle of mumps hepatitis clearly should be sought.

Summary and Conclusions

A case is presented in which a man in the course of a relatively severe mumps infection developed icterus, hepatomegaly, and blood biochemical alterations indicative of hepatic damage. It was felt that these phenomena were attributable to an infectious type of hepatitis and that the responsible etiologic agent was probably the mumps virus. The literature pertaining to jaundice or hepatitis complicating mumps is reviewed, and three previous cases of this nature are described. Evidence is adduced both from the medical literature and from personal studies that liver involvement is decidedly uncommon in mumps. Because of our present ignorance of this subject and the potential seriousness of any form of liver injury, further studies of the status of the liver during mumps are definitely indicated.

† References 1, 7, and 8.

Mrs. Elizabeth Martinsen, of the staff of the Armed Forces Medical Library, assisted in the review of the medical literature pertaining to this subject.

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Books

EDITED BY WILLIAM B. BEAN, M.D.

BOOK REVIEWS

Cold Injury: Transactions of the Third Conference, February 22, 23, 24, and 25, 1954, Fort Churchill, Manitoba, Canada, M. Irene Ferrer, Editor. Price, $4.50. Pp. 216. Josiah Macy, Jr. Foundation Publications, Post Office, Box 575, Packanack Lake, N. J., 1955.

The geopolitical changes taking place in the last twenty-five years have caused increasing numbers of men to change, willingly or unwillingly, their habitat to frigid areas of our planet. The international geophysical year scheduled for 1957 and 1958 will see hundreds of technicians and scientists residing temporarily in Antarctica in the greatest and perhaps most hazardous reconnaissance of unexplored areas of the globe in all of history. Flights into the upper atmosphere are already taking men into regions where they are exposed to extremes of low environmental temperature. We have learned much since World War II of the effect of cold on man, but there is much more that we do not know and must learn before man can successfully and safely live in the coldest reaches of our own planet or of outer space.

This book consists of the transactions of the third of five conferences on cold injury sponsored by the Josiah Macy, Jr. Foundation. It is of interest that the conference was held at Fort Churchill, Manitoba, Canada, during the severest period of the winter at this northern Canadian outpost and research center.

In addition to reports on fundamental research concerning cold injury, this volume contains several reports of clinical studies on man that should be of wide interest. The emphasis has been placed on the interrelationship of circulatory and metabolic factors and on diet in man's attempt to adapt himself to a cold environment and to avoid cold injury.

An excellent job of editing has been done by Dr. M. Irene Ferrer, and the printing and binding of the book have been done superbly.

This is an essential book for all who are seriously concerned with the effects of cold on man, and it should be of value to physiologists and to clinicians who have a special interest in metabolic and circulatory disturbances and diseases.

EDGAR A. HINES JR., M.D.

Kreislauf-Buecherei, herausgegeben in Verbindung mit der deutschen Gesellschaft fuer Kreislaufforschung. Band XIV: Die funktionelle Beurteilung des Lungen-und Herzkranken. By Dr. med. Heribert C. Landen. Price, DM 22. Pp. 166, with 75 illustrations. Dr. Dietrich Steinkopff Verlag, Holzhof-Allee 35, (16) Darmstadt, 1955.

This monograph describes a functional evaluation of pulmonary and cardiac disease by a spirographic method. This method was developed by Knipping, at the University of Köln, many years ago and was used recently more intensively by this group for cardiac evaluation. The first part describes the apparatus and the method of registration. The spirometer enables the observer to calculate the oxygen consumption directly from the graph during room air breathing and during 100% oxygen breathing by a simple switch to the oxygen tank. For exercise a hand-moved ergometer is used, which allows exact calculation of the work performed and automatic control of the work required from the patient.

Besides the determination of the conventional vital capacity and maximum breathing capacity, the so-called oxygen uptake deficit is tested at rest or during exercise. The oxygen uptake deficit is the difference between the oxygen consumptions while the patient breathes room air or 100% oxygen. In the presence of impaired oxygen diffusion through the lungs, the increased alveolar oxygen tension during 100% oxygen breathing leads to better diffusion and increased oxygen consumption. The authors prefer their method to the direct determination of the arterial oxygen saturation by needle puncture.

The same method can be used in bronchospirometry to determine separately the function of each lung.

The cardiac function is evaluated by determination of the maximal oxygen uptake during exercise. The oxygen uptake during the initial phase, the steady state, and the recovery phase are correlated in a so-called cardiac efficiency coefficient. In cardiac insufficiency the coefficient decreases in comparison to normals. The coefficient is believed to represent adequately the cardiac efficiency already at lower work levels than the maximal performance capacity of the heart.

The book contains several case reports to illustrate the practical usefulness of the method in the evaluation of patients with pulmonary and heart disease. The advantage of the method appears to be its simplicity and the possibility of repeating the test as often as desired. Its proper place of application is probably in the determination of borderline or minimal cardiac insufficiencies in patients with early symptoms and in the differentiation of cardiac from noncardiac symptoms in patients without definite evidence of heart disease. It is felt by most of the workers in this country that the determination of the maximal oxygen uptake and thus the maximal circulatory capacity is an all too vigorous procedure and cannot be applied in severer cases as represented by most of the clinical situations.

The monograph is well written and well illustrated and should be of value to those who possess good command of the German language and who are interested in cardiac function studies on a large clinical scale by a relatively simple method.

PAUL KEZDI, M.D.

Clues in the Diagnosis and Treatment of Heart Disease. By Paul D. White, M. D. Price, $5.50. Pp. 186, with 43 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1955.

The President's consulting physician—now well known for his open manner and forthright comments—comes forth with a digest of clues in the diagnosis and treatment of heart disease which is aimed specifically at the general practitioner but which will be greatly appreciated by internists and should be avidly perused by medical students. These clues originate from the history, the physical examination, the x-rays of the chest, and the electrocardiogram. Special diagnostic procedures, such as cardiac catheterization and angiocardiography, are mentioned but not discussed. There is special emphasis on these symptoms—breathing difficulties, pain, and palpitation—and on these signs—heart sounds, heart murmurs, and blood pressure.

Reading this book is a pleasure, not a chore. Its chief advantage is that the author gives his reader a personal, meaningful talk from his own practice experience. The disadvantage is that in making this type of presentation the various topics discussed are not treated in a complete fashion. Expert readers will find omissions of clues they would like to add, but this does not detract from the purpose of the book.

There are 43 well-chosen illustrations which add to its appeal. In addition to clues which help one arrive at a correct diagnosis, there is a section on therapeutic clues.

GEORGE E. BEDELL, M.D.

The Diabetic's Cookbook. By Clarice B. Strachan. Price, $6.50. Pp. 304, with illustrations. The Medical Arts Publishing Foundation, Houston, Texas, 1955.

In her introduction the author states that the purpose of her book is "to introduce variety or flexibility into the prescribed diet." To this end she has translated diet prescription to menu to recipe. The latter are arranged to fit the widely used ADA diet exchange lists, and each has appended its equivalent exchange value. The stated purpose has been admirably achieved. The physician may, with confidence recommend this book to the diabetic patient and the person who cooks for him.

ROBERT C. HARDIN, M.D.

Classics of Biology. By A. P. Suñer; translated by Charles M. Stern. Price, $7.50. Pp. 337. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1955.

To the physician not versed in systematic biology, whose knowledge of basic medical science is confined to what he may have learned in medical school, "Classics of Biology" should serve as a very satisfactory introduction. It differs from many anthologies in having fairly extensive introductory material written by the editor to introduce each

chapter. Here are spread before us in review a sample of the important work of men who are largely responsible for giving expression to stimulating ideas in biology. Many of the papers report studies or ideas which were turning points to new advances in the ever-increasing fields encompassed in the realm of general biology. Some of the chapters are entitled "Matter and Energy in Life," "Form and Dynamics of Reproduction," "Biocatalysts," "Heredity," "Geography and Palaeontology," "Causation and Design," "Reflexes, Consciousness and Will," "The Whole and Its Parts." We have ranged before us excerpts from classical essays in biology from Lavoisier to Schrödinger, from Robert Hooke to Sherrington, from Schwann and Virchow to Pavlov and Bergson. In addition to providing a very clear synoptical and speculative prologue for each chapter, many of the excerpts are unexpected in a book on biology, since they have never found their place in the orthodox medical curriculum.

This book brilliantly illustrates the very real importance of the individual scientist or biologist in advancing science. The correlary implication is that research by committees, though excellent for gleaning in territory harvested by great persons, is not likely to produce new ideas, ideas which are germinal and bring progress by reorientation and rearrangement of our concepts. The other general conclusion, repeatedly emphasized, is that even the science of biology is not enough—that we need to merge biology with philosophy in order to get a more comprehensive view of the impact of biology on contemporary life and the wide ramifications of this essential force. The editor has managed to string together on the thread of his connecting themes a handsome, indeed a magnificent, display of pearls from the realm of science and philosophy. The riches in this book are in fact a reassuring tribute to the capacity of the human intellect. Careful study of it might help alleviate some of the neurotic preoccupation with the harsh anti-intellectual and anti-scientific forces loose in the land today.

WILLIAM B. BEAN, M.D.

Kinships of Animals and Man—A Textbook of Biology. By Ann H. Morgan, Professor of Zoology, Mount Holyoke College. Price, $6.75. Pp. 839, with 576 illustrations. McGraw-Hill Book Company, Inc., 330 W. 42d St., New York 36, 1955.

The number of textbooks dealing with elementary biology is so large that it seems somewhat out of style to advocate that there should be a beginning course in zoology and another one in botany, rather than a merger of the two in a composite of biology that samples from both disciplines. It is, therefore, refreshing to encounter a new book whose focus is frankly on animals. It is not a small book, nor is it one that deals primarily with general principles or with animal types. "Kinships" is a book that contains the solid information that is the basis of any good zoological treatment. But, beyond this, there is fashioned a text that explains in dynamic fashion why animals are what they are, how they behave, and what their phylogenetic relationships to other organisms are. There are five major divisions, and these treat of the following topics: the cell; ecological relationships; tissues and organ systems; development; animal types; evolution and conservation. An appendix includes well-chosen lists of recommended readings. The book is rather well illustrated, but not lavishly so; it contains an adequate index.

To the physician who is willing to reorient himself away from an anthropocentric bias, who would be interested in animals considered as living organisms related to each other and their environments, and who appreciates entertaining scientific writing—to such, "Kinships" is recommended without qualification. It will provide enjoyable hours of good reading.

L. B. AREY

Comment: Those who read book reviews at all rarely get out of the narrow confines of their own specialty. This book on the "Kinships of Animals and Man" is an example of the kind of book which should appeal to physicians who want to read something apart from the straight and narrow path of internal medicine. It is only fair to state, however, that this book has been criticized by biologists as being a rather routine approach to biology rather than a new approach as suggested in the title. Maybe this means nothing more than that physicians should be more conversant with the field of general biology.

WILLIAM B. BEAN, M.D.

Handbook of Toxicology. Vol. 10. Acute Toxicities. Edited by William S. Spector. Price, $7. Pp. 408. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

This is the first volume of a comprehensive treatise on toxicology and includes the acute toxicity data on lethal doses of solids and liquids on laboratory animals as well as lethal concentration data for gases, vapors, and fumes. The compounds reported include many pure chemical compounds, and there is, as well, a detailed coverage of therapeutic medicinals. There has been an urgent need for this sort of compilation of toxicity data, and this volum should be a welcome addition to biological research laboratories everywhere.

CARL A. DRAGSTEDT, M.D.

Farmacologia: Materia médica y terapéutica. Volume I. By L. E. Camponovo and A. J. Bandoni. Price, not given. Pp. 644, with 7 illustrations. Lopez and Etchegoyen S. R. L., Junín 863, Buenos Aires, Argentina, 1955.

This is the first volume of a treatise on "Materia Medica and Therapeutics." It includes a consideration of the historical development of materia medica and pharmacology, the general principles of pharmacology, the forms of administration of drugs, the routes of administration, the technique of prescription writing, and a table of drug preparations and doses. Following this preliminary material there is the first section of systematic therapeutics which will be continued presumably in subsequent volumes. This section deals with parasites, both external and internal, and their remedies. The book is written in Spanish and reflects the viewpoint of the Argentine authors. If the volumes completing the set follow the example of the first volume, it would appear to be a useful reference as to therapeutics (more so than as to pharmacology) for the Spanish-speaking physician.

CARL A. DRAGSTEDT, M.D.

Cancer of the Lung: Pathology, Diagnosis, and Treatment. By Milton B. Rosenblatt and James R. Lisa. Price, $15. Pp. 330, with many illustrations. Oxford University Press, 114 Fifth Ave., New York 11, 1956.

A Quest into the Environmental Causes of Cancer of the Lung. U. S. Public Health Service Publication No. 452, Public Health Monograph No. 36. By W. C. Hueper. Price, not given. Pp. 54, with charts and tables. Government Printing Office, Washington, D. C., 1955.

The Statistical Study of Association Between Smoking and Lung Cancer. By Joseph Berksón. Price, not given. Pp. 30. Published in the Proceedings of the Staff Meetings of the Mayo Clinic, Vol. 30, p. 319, Rochester, Minn., 1955.

The clouds of smoke, the considerable heat, and the scanty amount of light surrounding the problem of cancer of the lung and its putative relationship to excessive cigarette smoking has added to the general pall of impervious haze which separates us from the truth. It also confuses and confounds the layman. We must remember that today the vast majority of physicians are laymen in fields away from their own particular specialty, even if their specialty be general practice. In this arena of semiorganized confusion we have excellent examples of passionate devotion to beliefs, of propaganda, both pro and con, and of the failure to obtain the massive and painstaking volumes of data required to extinguish the fire by smothering it or fan the embers into a flame which will cast light on the problem. We have seen a great number of vehement pronouncements claiming that cancer is caused by increased and excessive cigarette smoking because there is a statistical correlation between the rising incidence of cancer of the lung and the increased sales of cigarettes.

Rosenblatt and Lisa's book "Cancer of the Lung" is more a collection of essays by specialists than a comprehensive and unified treatise, although the names of Papanicolaou, Chevalier Jackson, Foot, Chamberlain, Daniels, and Roswit, in addition to the senior authors, are a roll call of great men in the field. This book is disappointing, and it is disappointing without having a major flaw. It is a matter of mood and emphasis. One difficulty is in bringing the contributions of a series of different authors from different disciplines into one cohesive and unified whole. The index is adequate, and one can find without difficulty a couple of pages devoted to pulmonary osteoarthropathy and clubbing.

But one wishes for emphasis on the occasional patient thought merely to have severe and painful arthritis who turns out to have osteoarthropathy as the clinical debut of cancer of the lung. One misses any emphasis on the vast production of ropy, glary mucus by patients with alveolar-cell carcinoma, patients who in a day may cough up a pint or quart of the most annoying and distressingly sticky sputum. There is relatively little emphasis on the clinical significance of metastases to the adrenals which, though rarely lasting long enough to produce full-fledged Addison's disease, frequently is severe enough to cause failure of the adrenal cortical function.

The outstanding feature of the book is its most excellent illustrations. No doubt this is responsible for the high cost, $15. The extensive discussion of surgical techniques has little interest for the internist. Thus the book is recommended as more valuable for the undergraduate student, the intern, and the resident than it is for the practicing physician who has had wide experience with disease of the lung.

The central problem which emerges from the text is that in spite of all of our diagnostic efforts, in spite of all the emphasis on cancer of the lung, the proportion of salvage is still hideously low. We need to face the fact that in our present society, without stronger public health compulsions or arbitrary centralized health authority, every citizen has the natural right to die of cancer of the lung. X-ray survey of the whole population is not a practicable answer. The suggestion that the family physician's office is our first line of defense is no doubt true. But it must be true also that the tendency for so many general practitioners to see a large number of patients reduces the likelihood of detecting many cases of early and operable cancer of the lung. The critical question, pending settlement of the mystery of causes of cancer of the lung, is how do we detect it early. In a democracy the only way is better trained and constantly alert physicians.

Hueper's book is a panoramic inquiry into the complexity of the environmental factors which may or may not be associated with cancer. Increasing experience with problems of industrial medicine, the toxic dusts, fumes, and smogs which darken the lungs of workers and darken the light of our cities, on these he bases his views in comprehensive panorama of the epidemiological, medical, and experimental data. These demonstrate that large occupational groups in the general population have prolonged and sometimes intensive contacts with one or several agents theoretically capable of inducing carcinoma. A number of charts of parallel and increasing incidence of tobacco consumption, carcinoma of the lung, coal production, petroleum production, and chemical production of one kind or another illustrate the complexity of parallelism. Perhaps the most cogent evidence brought forth by Dr. Hueper on the lack of demonstration of an etiologic connection between excessive cigarette smoking and carcinoma of the lung is found in the lack of correlation between cancer and cigarette cough, and the lack of finding carcinoma of the lips or tongue in excessive smokers whose mucous surface often is in contact with the potentially carcinogenic materials such as stain the fingers. Many other discrepancies are discussed. The experimental evidence regarding carcinogenic properties of tobacco tar is confined to the carcinogenic action of some cigarette tars in hyperreactive animals. There is no evidence that these observations on the skin of a strain of selective inbred mice have any equivalent in man. Thus the practical importance of these observations is at present uncertain. The final decision must be kept in abeyance. We must continue to get more data. The facts we have at the moment make it unlikely that cigarette smoking represents a major factor in the production of lung cancer.

Perhaps the most convincing evidence in the whole array is that adduced by Berkson in his searching critique of the statistical studies which have implicated excessive cigarette smoking as the cause of cancer of the lung. He demonstrates that what we really need is prospective and retrospective studies in population not preselected, in which the one variable, excessive smoking, is manipulated at the will of the experimenter. Here is food for mature reflection. But we need to remember that a most tantalizingly difficult clinical problem is here before us. We must recognize that while excessive smoking has not been demonstrated to be a cause of cancer of the lung. this negative evidence must not be construed as proving that it indeed is not a cause.

WILLIAM B. BEAN, M.D.

The Flavonoids in Biology and Medicine. By Maurice E. Shils, Sc.D., and Robert S. Goodhart, M.D. Price, $2. Pp. 101, with illustrations. The National Vitamin Foundation, Inc., 15 E. 58th St., New York 22, 1956.

This critical review by Shils and Goodhart should put a stop to a great deal of the unhappy confusion which has prevailed in our understanding of blood coagulation and vascular inadequacy in conditions where nutritional factors are supposed to have a role. Ever since Szent-Györgi suggested the possibility of flavonoids having some essential biological function in mammalian physiology, in 1936, there have been discordant reports, many of which are magnificent examples of the ease with which observers are distracted by uncontrolled experiments, particularly when these are superimposed on very extensive clinical ignorance. In all the vast pile of papers written in this field there is small residue of useful clinical information. We obviously need such critical reviews as this well-written and well-organized one. It is a sad reflection on the editorial judgment of the last 20 years to see how much space in respectable journals has been taken by studies devoid of adequate controls.

Some of the most valuable observations incorporated into this critical review are the negative results of unpublished experiments. This underscores the importance of negative results. While Shils and Goodhart render the conservative verdict of not proved rather than not guilty, their essay reveals how greatly the field of clinical nutrition has suffered in not attracting to itself a sufficient number of persons with inquiring and yet skeptical minds so notable in many other clinical fields, such as cardiovascular disease. An adequate table of contents takes the place of an index, which in a monograph this short is not a critical omission. It is to be hoped that the authors can extend their probing inquiry into adjacent areas in nutrition, for such critiques pave the way for a fresh start.

WILLIAM B. BEAN, M.D.

Medical Research: A Midcentury Survey. Vol. I. American Medical Research: Its Principle and Practice. Vol. II. Unsolved Clinical Problems: In Biological Perspective. Price, $15 for set of 2 vol. Pp. 765, 740. Published for the American Foundation, by Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

"Medical Research: A Midcentury Survey" has had many notable reviews in many notable medical journals as well as in newspapers and journals for the layman. Medical research is the biological focal point of our age, and the obsession of some has become the confusion of many. In an era of the increasing specialization necessary for the advancement of learning we all become separated from those at work in neighboring fields. The bane of specialization is not the narrow confines of our individual lines of attack, but the nasty fact the supreme or even merely satisfactory competence in any specialty puts one at risk of basking in the illusion that such special understanding encompasses other fields or all fields. We have deified the winner of a quiz program and neglected the scholar; we look to the Oscar winner or the champion athlete for oracular words on the significance of the atomic bomb or the motives behind the oscillation of Russian political schemes. As a people we are wary of thinking, afraid of the intellect, wishing hopefully that science with its machines and calculators may supplant the man of wisdom and give automatic answers. The grave hazard of our age of research and specialization inheres in the nearly universal failure to recognize that special knowledge does not automatically lead to general understanding. To get wisdom our learning must be broad as well as deep. We must know not just the situation of the present moment, as one entering a strange play or movie in midcourse. But the foundations of science, the history which is science, we must know. Any alert citizen of today and any physician who wishes to be more than the mechanical middleman who practices pushbutton therapy or the expert accountant who shuffles all the laboratory reports till he can force them into some fanciful pigeonhole called "the diagnosis" must read the two volumes entitled "Medical Research." They must be read, marked, learned, and inwardly digested.

Among the many difficulties soon apparent to those reading Volume I will be the literal impossibility of comprehending, assimilating, and then resynthesizing all the medical research going on in the country today. A corollary is that however much this book looks to the future, this can be done only in terms of the past. It is necessarily historical in its retrospective view. It considers things accomplished and things going on

but cannot, in the nature of things, tell us what will come. This is inevitable in material assembled by established administrators, scientists, and institutions, for by the nature of being established one is certainly aging and perhaps old. Information in the book has been obtained from a vast number of separate interlocking or overlapping agencies, institutes, foundations, governmental divisions, medical schools, private industrial corporations, and the like. It presents a splendid panorama of the complex interweavings of this great multitude of institutions whose aim and purpose it is to foster medical research in one form or another. For the first time I can understand some of the structure of the organized medical research effort.

Even more important is the recognition that much of the organizing impetus is held in a rein loose enough to enable individuality to survive. Not much emphasis is given to the threat inherent in any institution—that it comes to live in and for itself, losing sight of the purpose for which it was built. There is the same final limiting factor on administration and administrators, that they devour everything in overhead and have nothing left for work, just like the end-point in the architect's nightmare of the lofty magnificence of skyscrapers grown so enormous that they are all elevators with no room for offices. The lesson to learn is that complexity of institutions tends to proliferate and needs constant pruning. Too many plants may choke each other and all wither.

Volume I by itself would be a great achievement. While sensing possible abuses and dangers, we may look with pride upon the intricate structure of the industrial, federal, state, and private foundation, the voluntary health agency, the medical school, the hospital complex in which medical research, as we know it, has been able to reach such heights. To be able to show the four-dimensional intermingling of such diverse forces is a major accomplishment. We should not forget the fact that without the American Foundation this study would not have been made—a vivid example of the importance of having such altruistic foundations use their endowments wisely.

One frustration at our inability to communicate one with another is moderated by such a book as Volume II entitled "Unsolved Clinical Problems: In Biological Perspective." In the chapters of this book, indications of the rapid movement forward in various fields of science during the past half century form an exposition of the present state, plight, or problem. These are set forth with clarity, brevity, and an amazing mass of technical detail, without recourse to charts, graphs, photographs, or square-root symbols to give the leverage to force unruly data into some pattern, either predetermined or just pretty. The book begins with a chapter entitled "Metabolic Concepts Orienting Research in Biology and Medicine," and its theme considers normal physiological functions or manifestations of the molecular changes that are metabolism and disease as a constellation of disturbances of finely integrated chemical mechanisms. Enzymes and coenzymes, metabolic pathways, cellular homeostasis, assimilation, storage and transformation of chemical energy, and all the vast interrelationships of metabolic life provide emphatically a recurring demonstration that to understand symptoms and manifestations of disease presupposes an understanding of biological activity in terms of its molecular mechanisms. Energy transformations are coterminous with life.

To choose any one of the nine chapters for comparison with another is not very helpful. They are all well done. In this predicament a reader finds that he gets most from those he knows least about. For instance, the chapter on schizophrenia is a classical example of the insight of illumination brought by the skillful blending of facts, hypotheses, and observations mastered, compressed, selected, and described in lucid style. The emphasis on the organic, biological orientation to mental disease is singularly appropriate at a time when we see the decline of systems of belief, the mystical formulations of those who erect beautiful hypotheses but deny the possibility of testing them by the rubrics of science. The coming of the chemist and pharmacologist into the locked mind of traditional thought in psychiatry and psychoanalysis brings the hope that progress will come through new insights, expanding and enlarging old concepts and discarding what is ineffectual or reactionary. In the practical world of today, where mental and emotional disorders vex worried and frustrated people, we must use every relevant fact and each idea or method in accordance with its use in predicting and its clue to treatment.

If the chapters are uneven in temper and in clarity this mostly reflects the nature

of the problems and the state of our knowledge and ignorance in different fields. It is impossible to compare cancer, arteriosclerosis, rheumatism, sterility, hypertension, viruses, alcoholism, tuberculosis, and schizophrenia. In the areas where I have experience I find factual errors very rare. These critiques are models of their kind. The American Foundation, its editor Esther Everett Lape, and her associates have been well served by the board of twenty-six distinguished scientists who have served as consultants, and they have been used wisely and well.

It is not to be expected that any book will be better than its authors, nor any description and analysis of research today better than it is in fact. The outlook and forecast are those of the eminent authorities who have banded together to provide the basic material from which this book was constructed. In the light of the magnificient accomplishment, recognizing the real need for every physician to read this book, and in a spirit which is neither mean nor little, I take issue with the underlying theme presented in the introduction which describes the aims and methods of study. On page xxvi, "Concepts and Methods that Guide the Study," and to the end of the chapter is expressed a point of view which probably could come only from someone not personally connected with science. At the same time it is very idealistic. Its essence is that all discovery represents a synthesis of effort, that the man is inconsequential, and that the idea is everything. The editors are apprehensive about the historical technique of using dates and persons in giving credit for discovery. While it is perfectly true that the seeds of later accomplishment often lie in barren periods between the dates of significant discoveries and are unknown to vast numbers of anonymous investigators on whose shoulders we all stand, many scientists will deny that science can be stripped of its personalities, with ideas embodied in some kind of ectoplasmic mist. My view is that all biology would lose much of its motivating incentive of curiosity if it were not ultimately aimed at understanding human life. In like manner, the notion of abstract ideas and science as separate from individual investigators, and research in the abstract, makes no sense to me. Furthermore, this avowed principle is carried out very erratically in the various articles in the text. In some chapters the name, initials, and frequently the institution of an investigator are set forth. In others simply the name Smith occurs or no name at all. This is all well and good if you happen to know who Smith is and where he is, but it doesn't mean very much to the critical investigator who knows that there are a lot of Smiths and that the work of one is not as good as the work of another or the word of one to be relied on as much as the word of another. That personality has to intrude may be less than nice and neat, but being distasteful to some makes it not less true. There will be some annoyance that some minor worker is mentioned four times and others not at all by name or deed. But since this study could not be comprehensive, we condone inconsistency.

My own experience with investigators has been fairly wide. I have never seen any indication of the passionate desire for anonymity on the part of those engaging in research. On the contrary, we all know examples of people so obsessed with the importance of acquiring fame that their enthusiasm may outmarch their data, and their claims outstrip their facts. While this is deplorable, I do not see that science could well get along without recognition and praise distributed among the workers. We know of people who have been praised for the work done by others, but we know of many, many more who receive due credit for what they themselves have done. Nowhere is this more important than the subtle realm of ideas. For we have no clear notion of the almost mystical and mysterious ways in which genius can weave diverse and seemingly unrelated threads into a marvelous pattern where before only a great snarl and tangle had existed. Since we are able neither to breed up genius nor to predict it, it is worth while to be able to identify it and praise it, not so much in adoration of ideas as such but a respect and recognition of the person who happens to harbor splendid capacities.

While it is very difficult to give credit to institutions, perhaps the fact that the editor realizes the importance of people and names is the ambivalence of the last paragraph of the introduction: "Our concern in this study has been with concepts rather than persons; while we have been driven to the use of many names, for lack of a better device, we have used them rather to identify lines of work rather than to attribute credit. If injustices have been done—as in some cases they inevitably must have been—it will not

greatly matter in the record where the dominant interest is recognized by all of us to be not the workers but the work."

The complaints represent a singular but not grievous flaw in the book. Were the theme actually embodied in the various monographs and were there no incentive of recognition, science would suffer.

The greatest intellectual difficulty of our time resides in the inability of many people, often brilliant and extremely well trained and capable, to distinguish the subtle but absolutely essential difference between concepts, words that describe concepts, and things. An example of such behavior is seen in many scientific papers which begin with a perfectly legitimate hypothesis and then proceed to make the assumption that the hypothesis is a demonstrated fact.

I cannot think of scientific work as detachable from the person doing it, or even the team, or department, or group, or school. This is not to say that credit is ever apportioned with exact and inevitable justice—but often things come out with surprising equalization. Now it has been said many times over that credit for discoveries goes not to the man who had the original idea but to the man who comes along and dots the i's and crosses the t's, or to the man who sells the idea to the public, or to the man who is most convincing in his description of it. Sometimes it may go to those who talk most loudly and for the longest time.

What fruitful use might be made of these notable volumes? For those with a practical turn of mind, Volume II provides new critical insights into a pleasant multitude of perplexing medical problems which are of the greatest practical importance. In the modern world of busy practice, many physicians have lost the habit of reading, others have never cultivated it, and few can or will make the sacrifices of time and effort needed to know what goes on in the world they live in. They feel lucky if they can keep up with their own special interests along ever narrowing lines. It is shocking but rarely recognized that specialists in medicine behave like bewildered laymen in other fields of medicine and science than their own. The monographs in the second volume of "Medical Research" provide a wonderful antidote for the poison of ignorance which we have to accept as the inevitable byproduct of specialization.

I must lament the lack of a bibliography. No doubt it would have been bigger than the two books themselves. The anonymous form in which the book is written is a handicap. The necessarily selective approach means that many people and institutions omitted from the personal mention which bulks so large in the book will be offended. It simply is not a fact, as the editors hope, that institutions, movements, and large-scale designs provide the moving force in research. The moving force is, and always has been, individual people. People contribute to the advance of research more by their individuality than by their conformity. The lack of an index severely limits the usefulness of these books for reference. Of course they should be read from cover to cover, but going back to pick up a detail, or a lost thread, is hard without an index.

I was troubled by the erratic interpolation within parenthesis of a date (1956) indicating when work had been done or published, or when ideas were prevalent. With no references and no index, this at least gives us our bearings; but it strikes me as an awkward usage. I have no suggestions for improving it.

These books should be known to and read by all physicians, by all thoughtful educators in schools to which physicians go for their preprofessional training, and by directors of institutions of higher learning. The recurring problems common to all universities are not peculiar just to medical research or to medicine. This book has not reached the attention of the great republic of physicians perhaps because the lines of communication have now broken down. It is the exceptional rather than the ordinary physician who reads (1) book reviews and (2) books which are not immediately applicable to his own particular and usually limited sphere of interest. A series of leading articles in the *Journal of the American Medical Association* might have got this a wider reading. I doubt if book reviewing, at least with the present audience, is an effective means of getting this message to its proper consuming public, the practicing physician.

Despite what I conceive to be certain small blemishes, these are notable books, grand in conception and monumental in achievement. Every literate physician will be the better for their careful and critical study, every citizen of the world might understand himself and his

times better for close reading of both volumes. In medical research as in science generally the past holds the seeds of the present and the present holds the seeds of the future. "Medical Research: A Midcentury Survey" stands astride the present, born of the past, looking to the future. Read, mark, learn and inwardly digest these books.

WILLIAM B. BEAN, M.D.

Growth and Development of Dental and Skeleton Tissue: Clinical and Biological Aspects. Report of the Seventeenth Ross Pediatric Research Conference. Price, not given. Pp. 78, with 22 illustrations. Ross Laboratories, Columbus, Ohio, 1956.

"Growth and Development of Dental and Skeletal Tissue," the subject of the Seventeenth Ross (formerly M and R) Pediatric Research Conference, is essentially a first step in mobilizing the newer studies bearing on the pathogenesis of dental caries. In developing this theme, the conference goes back to fundamental causes. Its discussions deal with the physiologic, anatomic, and pathologic properties of osseous and dental tissue as they evolve through genetic, nutritional, endocrine, anthropologic, and biochemical influences.

There is some discussion of the clinical application of these studies. Paget's disease, osteogenesis imperfecta, osteoporosis, and hyper- and hypo-parathyroidism are briefly discussed. Dental caries, as a clinical entity, naturally has a prominant place in the discussion. Other matters of clinical interest are the identifying of teeth as a specialized form of bone, the concept of bone mineral not as a static stone but as a dynamic system with an important homeostatic function, and the relation of dental caries to general health. While points such as these give a clinical flavor to the report, it remains basically a research conference at the exploratory level.

The book may not have a wide appeal among practicing physicians and dentists, but it contains much of value to them as well as to research scientists. It should play a part in bringing the dental and medical professions closer together in the fight on dental caries. Ross Laboratories are to be commended on attacking this universal problem in so fundamental a manner.

JOHN LESTER REICHERT, M.D.

In the Doctor's Office: The Art of the Medical Assistant. By Esther Jane Parsons. Price, $3.95. Pp. 312, with illustrations. J. B. Lippincott Company, 227-231 S. 6th St. Philadelphia 5, 1956.

From her own wide experience as a "medical assistant," the author has gained a deep insight into the responsibilities and problems of those who work in any capacity in the busy doctor's office. In addition, she has included in this book the suggestions made by a great many doctors themselves as to how their secretaries, receptionists, nurses, and technicians could be more helpful to them. For the technician the emphasis is especially well placed on the importance of laboratory hygiene and of absolute accuracy of procedures, with definite detailed lists of duties and the most efficient way to carry them out. For the secretary the needed emphasis is given to discreetness and integrity, without which poise and intelligence are of little value. In the matter of secretarial duties, however, the recommendation that drafts be made for important medical letters does not seem compatible with the special skill that one now has the opportunity to acquire in training for such a position in the modern doctor's office. Although this book is a second edition, the author has clung to a few expressions that seem rather stilted, particularly those used in describing public relations situations in the office. After a thoughtful reading of "In the Doctor's Office" by any girl who works there she will be aware of the need for improving her efficiency and also for using the proper degree of courtesy and restraint in her relations with patients. She will be impressed by the fact that the ethical standards of the medical profession apply to "medical assistants" as well as to the doctors for whom they work.

MYRETA ESHOM

Klinische Elektrokardiographie. By Dr. Max Holzmann. Price, $19.05. Pp. 688, with 303 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N., and Intercontinental Medical Book Corporation, 381 Fourth Ave., New York 16, 1955.

This is the third edition of one of the leading standard works in electrocardiography in the German language. It is a practical textbook viewed with the eyes of the clinician.

The reader will find the large amount of clinical material often backed with autopsy findings and with good cross references to experimental literature. The description is on a high level, with strong scientific criticism, also presenting controversial material. The usual subject matter is covered completely. The theoretical part, including chapters on historical introduction, apparatus and equipment, electrophysiological basis and description of normal ECG, is given in one hundred sixty pages. The longest chapter, three hundred pages, deals with the abnormal ECG, excepting disturbances of the rhythm, which are outstandingly described in a chapter of one hundred seventy pages. Vector analysis and vectorial synthesis in the three planes are presented in an understandable manner and with special emphasis on positional changes in the ECG. The description of the ECG of coronary insufficiency and pericarditis is more detailed than in other books of similar volume. In the chapter about toxic, infectious, and allergic injuries to the myocardium the author tries to specify more precisely the German term "Myocardschaden." The attempt to justify this term as having specific and practical value should be considered as progress, even if it might meet criticism in the literature of this country. Also, a longer discussion of ECG of the congenital heart, of the mitral stenosis heart, and of abnormalities of the atrial ECG adds to the value of the book. The bibliographic references are appended to each chapter. They refer very well to the most important papers in world literature. The text is printed on good paper and is well illustrated, except that there could be a greater number of unipolar ECG leads in some of the illustrations. The book will be more valuable to the internist and cardiologist than to the medical student or practitioner.

PAUL SCHIMERT, M.D.

Henry Ford Hospital International Symposium on Cardiovascular Surgery: Studies in Physiology, Diagnosis and Techniques. Proceedings of Symposium held at Henry Ford Hospital, Detroit, Michigan, March, 1955. Edited by Conrad R. Lam, M. D. Price, $12.75. Pp. 543, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1955.

In March, 1955, the Henry Ford Hospital sponsored a Symposium on Cardiovascular Surgery which was attended by 478 doctors from thirty-five states and twenty-two foreign countries. Many prominent physicians working in this field attended, presented papers, or entered into discussion of the various topics covered. Dr. Conrad Lam has done us the great service of getting all of the remarks of this symposium into a volume which makes very exciting reading, indeed. The subject matter includes cardiac catheterization, the electrocardiogram in congenital vascular disease, angiocardiography, the diagnosis and treatment of pulmonic stenosis, adjustments between systemic and pulmonary circulation, evaluation of transposition operations, mitral valve disease, aortic valve disease, septal defects, cardiac arrest, hypothermia, and diseases of the aorta. Besides the manuscripts of formal papers presented at the symposium, this volume contains spirited discussion on the several methods of approach to certain problems on which doctors are not in agreement. Beautifully and abundantly illustrated, this book is a must for doctors interested in cardiovascular surgery.

GEORGE N. BEDELL, M.D.

News and Comment

ANNOUNCEMENTS

Course in Interpretation of Complex Arrhythmias.—A course in Interpretation of Complex Arrhythmias will be given at Michael Reese Hospital by Louis N. Katz, M.D., Richard Langendorf, M.D., and Alfred Pick, M.D. This is an advanced course intended only for experienced electrocardiographers. The class will meet daily from 9:00 a.m. to 5:00 p.m., Dec. 3-7, 1956.

Further information and a copy of the lecture schedule may be obtained from Secretary, Cardiovascular Department, Medical Research Institute, Michael Reese Hospital, Chicago 16.

Ninth International Congress on Rheumatic Diseases.—The Ninth International Congress on Rheumatic Diseases will be held at Toronto, from June 23 to 28, 1957. This quadrennial function of La Ligue Internationale contre le Rheumatisme will be held under the auspices of the Canadian Rheumatism Association.

The Program Committee invites contributions to the scientific program of the Congress and is anxious to receive reports on current clinical or basic research dealing with any aspect of the rheumatic diseases.

Those offering papers for consideration should submit a 200- to 300-word abstract not later than Jan. 1, 1957. Abstracts should be submitted in triplicate in the language in which the paper is to be read. If an abstract is submitted in a language other than English, it will be helpful, though not essential, if it can be accompanied by an English translation.

All correspondence should be directed to The Ninth International Congress on Rheumatic Diseases, Post Office Box 237, Terminal "A," Toronto, Ont., Canada.

Meeting of The American Psychosomatic Society.—The American Psychosomatic Society will hold its Fourteenth Annual Meeting at Chalfonte-Haddon Hall, in Atlantic City, on Saturday and Sunday, May 4 and 5, 1957.

The Program Committee would like to receive titles and abstracts of papers for consideration for the program no later than Dec. 1, 1956. The time allotted for presentation of each paper will be 20 minutes.

Abstracts, in sextuplicate, should be submitted for the Program Committee's consideration to Dr. I. Arthur Mirsky, Chairman, 551 Madison Ave., New York 22.

Van Meter Prize Award.—The American Goiter Association again offers the Van Meter Prize Award of $300 and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association, which will be held in the Hotel Statler, New York, May 28, 29, and 30, 1957, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations, should not exceed 3000 words in length, and must be presented in English. Duplicate typewritten copies, double spaced, should be sent to the Secretary, Dr. John C. McClintock, 149½ Washington Ave., Albany 10, New York, not later than Jan. 15, 1957. The committee who will review the manuscripts is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the winning essay by the author if it is possible for him to attend. The essay will be published in the annual proceedings of the Association.

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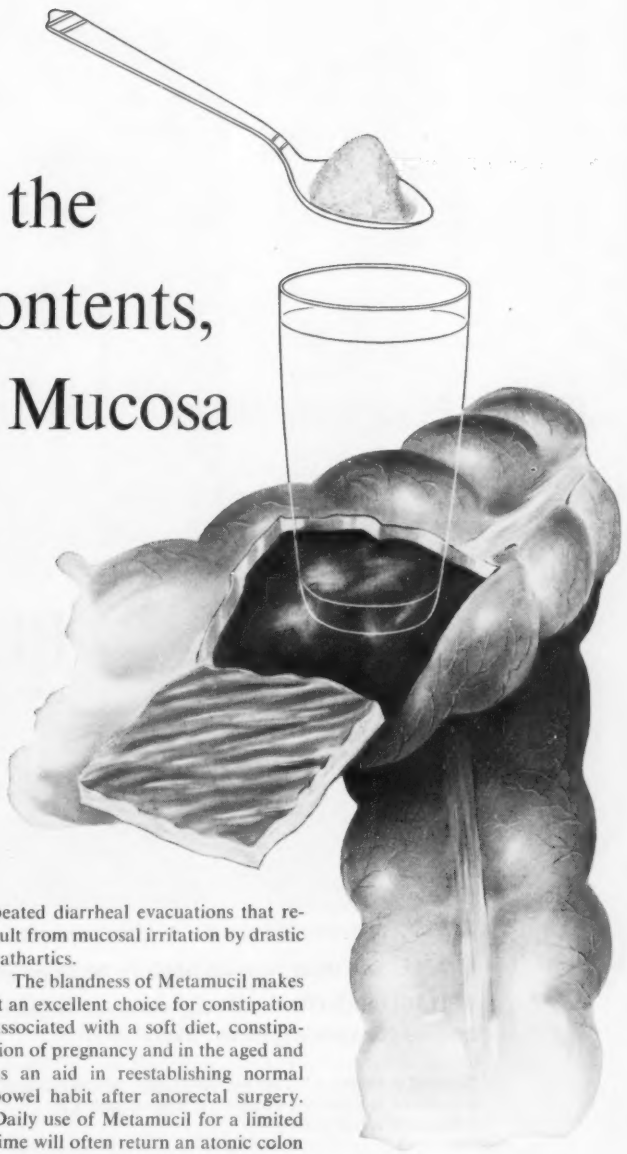

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In the milling, the oats—after being mechanically freed from extraneous material—are mildly processed at temperatures not to exceed 200° F., then cooled and hulled. The resulting "groats" are steamed and rolled to form standard oat flakes. For quick-cooking thinner flakes, the groats are cut into 2 to 4 pieces before steaming. The parts richest in vitamin concentration—the germ and the outer cellular layers of the oat seed—are retained, and remain virtually unchanged in vitamin values.

Cooking of oatmeal in the home leads to no appreciable vitamin loss. According to a symposium, prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association, "one hundred and twenty minutes' cooking in a double boiler did not cause any appreciable loss of thiamine from rolled oats."[2]

Quaker Oats and Mother's Oats, the two brands of oatmeal offered by The Quaker Oats Company, are identical. Both brands are available in the Quick (cooks in one minute) and the Old-Fashioned varieties which are of equal nutrient value.

1. Maynard, L.A., and Nelson, W.L., in Handbook of Nutrition, American Medical Association, ed. 2, Philadelphia, The Blakiston Company, 1951, p. 625.
2. Aughey, E., and Daniel, E.P., cited by Maynard, L.A., and Nelson, W.L.: Foods of Plant Origin, ibid.

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*DESSERT B	100	2.32	1.89	17.72	76	43	25 (USP)	0.160
*DESSERT C	102	2.4	3.2	16.5	75	69	228	0.110
**RENNET-CUSTARDS (average of seven flavors)	96.5	3.2	3.6	12.7	123	102	175	0.164

*Nationally distributed "ready-to-serve" dessert.
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1. Abramson, Julius; Bresnick, Elliott; and Sapienza, P.L.: *New England Jour. Med.*, 243:44, July 13, 1950.
2. Conybeare, John; and Mann, W.N.: Textbook of Medicine. Edinburgh, E. & S. Livingstone Ltd., 10th ed., 1952, p. 443.

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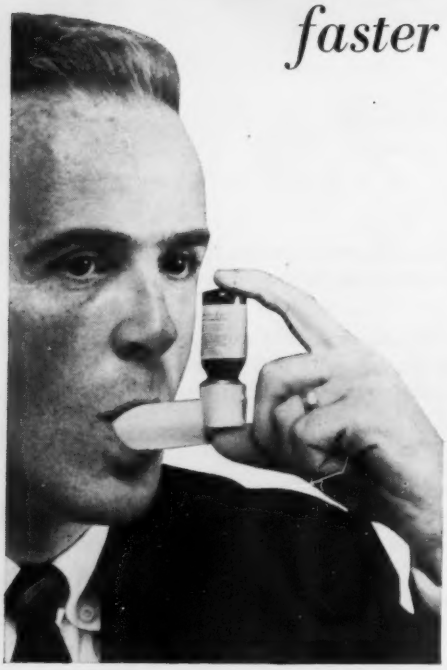

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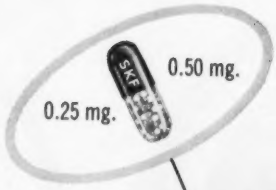

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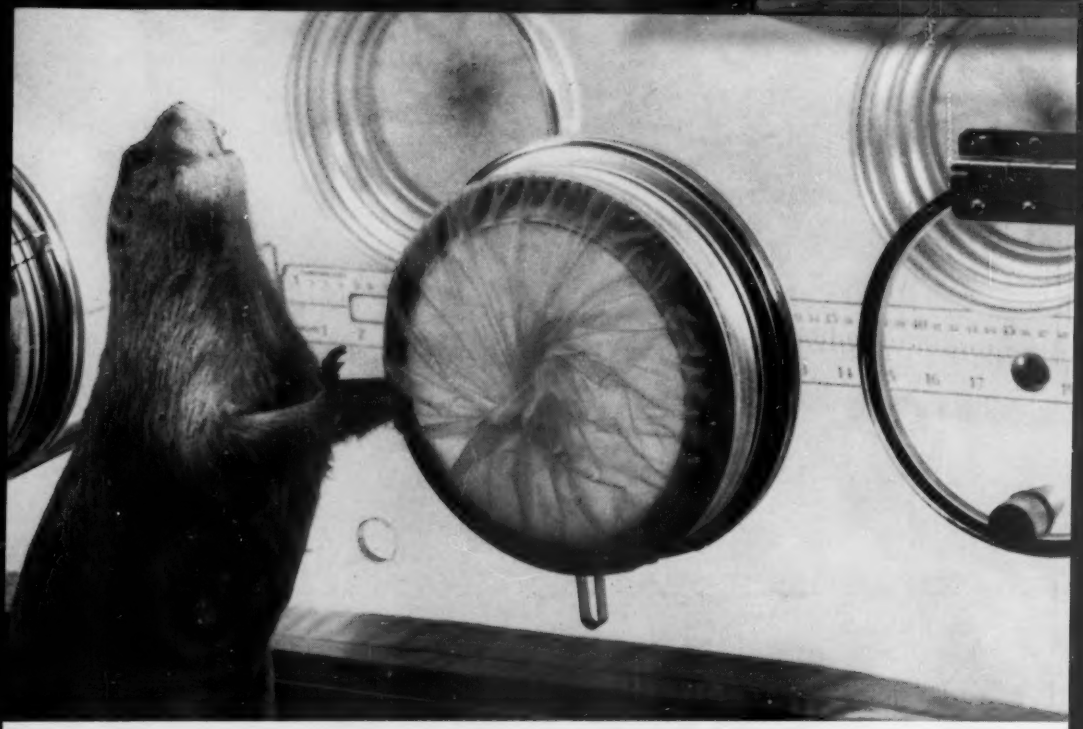

the gopher and the empty incubator

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Why the gopher? This rodent has an intriguing characteristic: at maturity, the pubic symphysis of the female is completely resorbed. Studying this process, Hisaw first came to suspect the existence of a relaxation hormone and eventually to discover relaxin.[1-3]

Hisaw's work led Warner-Chilcott research workers to the development of Releasin (a purified relaxin preparation). Releasin has proved a well tolerated and effective aid in controlling premature labor occurring between the 29th and 36th week of pregnancy.[4-6] When used early enough, Releasin can halt premature labor in many cases. Frequently, enough additional time *in utero* may be gained to permit delivery of a viable fetus.

Complete literature available on request.

References: 1. Hisaw, F. L.: Physiol. Zoöl. *2*:59 (Jan.) 1929. 2. Hisaw, F. L.; Meyer, R. K., and Fevold, H. L.: Proc. Soc. Exper. Biol. & Med. *27*:400 (Feb.) 1930. 3. Hisaw, F. L., and Zarrow, M. X.: Vitamins & Hormones *8*:151, 1951. 4. Perkoff, G. T., *et al.*: J. Clin. Endocrinol. & Metab. *14*:531 (May) 1954. 5. Abramson, D., and Reid, D. E.: J. Clin. Endocrinol. & Metab. *15*:206 (Jan.) 1955. 6. Eichner, E.; Waltner, C.; Goodman, M., and Post, S.: Am. J. Obst. & Gynec. *71*:1035 (May) 1956.

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. . . her fears of crowds and cancer ceased to worry her[1]

case report

patient:

"40-year-old woman with overt anxiety symptoms . . . marked fear of crowds . . . phobic ideas concerning cancer. Tension, irritability, and tiredness were in evidence."

medication:

'Thorazine', 25 mg. orally, t.i.d.

response: "Following ['Thorazine'] medication she became placid, composed and cheerful. When asked about her fears, she smiled and readily stated that they had ceased to worry her." She is now running her household for her husband and young son without difficulty.[1]

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is available in ampuls, tablets and syrup (as the hydrochloride), and in suppositories (as the base).

'Thorazine' should be administered discriminately and, before prescribing, the physician should be fully conversant with the available literature.

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1. Silverman, M.: J. Ment. Sc. *101*:640 (July) 1955.